

The Many Facets of the Myopic Eye: A Review of Genetic and Environmental Factors.

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Emmetropization during early childhood and subsequent eye growth eventuating in myopia are determined by both inherited and experiential factors [1-3]. The high prevalence of myopia and its prominence as a public health problem emphasize the importance of gaining increased understanding of the visual signals that govern eye growth, which may point the way toward possible methods of control and prevention. This chapter summarizes the current state of knowledge of this refractive state, emphasizing research on human subjects. Extensive reviews of research using animal models to study mechanisms underlying myopia are found in Norton [4], Wildsoet [5], and Smith and Hung [6].

Prevalence of Myopia

A comprehensive summary of the prevalence of myopia is contained in a recent paper [7]. As the paper notes, the lack of standard criteria for defining myopia makes it difficult to compare prevalence rates across studies. It is quite clear, however, that the prevalence of myopia is higher in Asia than in other parts of the world. For example, more than 75 percent of 18 year-olds in Taiwan are myopic [8].

The most commonly quoted value for prevalence of myopia in the United States, 25%, is from a nationwide survey in 1971-2 on 7401 individuals aged 12 to 54 years [9]. This study is now quite old, and more recent population-based studies show a higher prevalence, at least in some age groups. Intriguing evidence that the prevalence of myopia in the United States is increasing is provided in three recent large-scale studies [10-12]. These studies show increased prevalence of myopia in more recent birth cohorts compared to older ones. In the Framingham study [10], prevalence of myopia decreased from about 60 percent in 23 to 34 year-olds, to about 20 percent in people over 65. The Katz et al study [11] is a population-based sample of slightly more than 5000 subjects older than 40 years residing in the Baltimore area. Myopia declined with age and increased with increasing years of education.

The study by Zadnik et al [12] suggests that changing ethnic demographics, mainly increased numbers of Asians in Orinda, California, may account for the increase in myopia over the past 40 years. Using the same criterion for myopia (at least -0.50D in both meridians), prevalence for thirteen year-old children has grown from 12 percent to 28 percent. In addition to changing demographics, another possible reason for the increase is more near viewing activities, including reading and computer use, in the current generation of young people. However, in this study, near work assessed by questionnaires was not as great a risk factor as parental myopia.

These studies lead to the obvious question: Does myopia in individuals decline with age, perhaps due to a decrease in the power of the aging lens, or is there more myopia in more recent birth

cohorts? To provide a definitive answer, longitudinal studies are required, and thus far, there are only limited longitudinal data.

Genetic Origins of Myopia

Compelling data show that susceptibility to myopia is inherited. Increased prevalence of myopia has been found in children of myopic parents [13-16]. Twin studies comparing the incidence of myopia between monozygotic and dizygotic twins have suggested a higher concordance between monozygotic twins, consistent with a significant genetic predisposition to myopia [17-19].

Although there is good evidence to suggest that myopia is an inherited condition, a simple mode of inheritance or a single underlying susceptibility gene is unlikely. The variability in the rate of myopic progression, the variation in the extent of myopic development, and the prevalence of the condition suggest that more than one gene may be involved in the process [20]. Environmental factors, and their likely contribution to the process, complicate the analysis. A complex inheritance of the condition is also suggested by reports of a variety of inherited forms of myopia including autosomal dominant, autosomal recessive, and X-linked inheritance [14, 21, 22].

Involvement of multiple genes in the pathogenesis of myopia is supported by results of recent investigations. Three genomic regions, Xq28 (MYP1) [23]; 18p, (MYP2) [24]; and 12q, (MYP3) [25] have been shown to segregate with myopia in a small number of independent families. The chromosome 18 and 12 regions were identified using families with high myopia (more than 6.00D). A recent investigation of factors that regulate the rate and duration of eye growth in the mouse has also revealed two loci (Eye1 and Eye2) that may be responsible for genetic factors influencing myopia [26]. Some forms of severe myopia may be inherited as autosomal dominant or recessive traits. However, the majority of myopic individuals have a moderate refractive error that is more likely to be the result of a combination of genetic and environmental influences.

A recent study examined parental history of myopia in relationship to juvenile-onset myopia (onset before age 16). Pedigrees affected by juvenile-onset myopia also were analyzed [16]. Results showed that the odds of children with two myopic parents becoming myopic were 6.4 times those of children with one or no myopic parents. A pedigree analysis indicated that 63% of individuals at risk for developing juvenile-onset myopia actually became myopic, with an equal number of affected males and females. These results suggest that juvenile-onset myopia may be inherited as a complex trait.

Infantile refractive error also was found to be associated with juvenile-onset myopia [16]. The odds of developing myopia for children who had refractions in the lower half of the distribution at 6 to 12 months of age were 4.3 times those of children who had refractions in the upper half.

Environmental Factors

The role of near work

Since myopia in animal models is induced through manipulation of the visual environment, claims of a connection between human and experimental myopia have traditionally invoked the basic environmental theories associating excessive near work with the development of myopia. Direct evidence that near work in humans causes myopia is difficult to obtain. However, strong evidence of an association between the two is provided by epidemiological studies of subjects with similar genetic backgrounds, which demonstrate a marked increase in the incidence of myopia in individuals subjected to increased reading demands. For instance, in a study of Jewish families, the incidence of myopia for children attending orthodox high schools was 36.2% for

females compared to 81.3% for males [27]. The number of study hours per school day was 16 hours for the males versus 8 hours for the females. The incidence of myopia in Jewish children from the same geographical area who attended regular (6 hours per day) schools was 31.7% and 27.4%, for females and males respectively. In addition, the degree of myopia was three times greater for the males attending orthodox school than males in regular schools. Onset and continued progression of myopia also has been shown to occur in older adults who are in near work intensive occupations. By biometric analysis this incipient myopia was shown to be axial in origin, thus anatomically similar in expression to juvenile-onset myopia [28].

Causal mechanisms proposed to explain the relationship between near work and myopia have included neuronal, hormonal, mechanical, oculomotor and optical. It is beyond the scope of this paper to review all of these theories (but see [1]). While each may play some yet undefined role in the development of myopia, the greatest concordance of evidence points towards certain oculomotor parameters which are frequently associated with myopia.

Oculomotor parameters

Most studies concur that the oculomotor parameters associated with myopia include higher nearpoint esophoria, higher AC/A ratios, low accommodative response, low tonic accommodation, and higher post task open loop and closed loop accommodative hysteresis with longer delay constants, as detailed below. For many parameters, these abnormalities have been shown for myopia at any age of onset. Many of these parameters are physiologically inseparable from each other, that is, the presence of one predicts the presence of the other. This may suggest normal relationships in a system with a constant bias. This bias may be mediated by environmental and/or genetic factors. Longitudinal studies which track each of these oculomotor components may answer the question of whether one abnormal parameter creates the constant bias and triggers the cascade of related oculomotor findings. Alternatively, if certain parameters present simultaneously, an inherent synkinesis may be present. The outcome from these abnormal parameters may be that myopes experience prolonged periods of retinal blur. The chronic blur may produce axial myopia, as has been demonstrated in experimentally induced myopia in animals [4].

Phorias

There is a suggestion in a limited number of studies that nearpoint esophoria precedes the development of myopia [29-31]. Continued esophoric shifts have been shown to occur while the myopia is progressing [32]; and a higher rate of myopic progression has been linked to children with esophoria [29]. In contrast, myopes whose refractive error had stabilized showed an exophoric shift that continued for two years before leveling off [34].

AC/A ratios

Higher AC/A ratios (the interaction between accommodation and vergence) are associated with the presence of myopia. Response AC/A ratios, calculated using measures of accommodation rather than the stimulus to accommodation, were found to be significantly higher in recent onset myopes of any age than in emmetropes [33, 35, 38]. Higher AC/A ratios were found in younger myopic subjects [33] and among those with lower amounts of myopia [35]. The myopia in these subjects may still be progressing, suggesting that higher AC/A ratios may be characteristic of myopic progression. They also may be found prior to the onset of myopia. AC/A ratios greater than 7/1 have been reported to be a risk factor for the development of myopia [35]. Supporting this is a study by Jiang [37], investigating response AC/A ratios in recent onset myopes and in emmetropes who became myopic over a 3-year period. The recent onset myopes (70% who continued to progress) and the emmetropes who became myopic had higher AC/A ratios than the

emmetropes. While the results were significant, the study was limited by a small number of subjects.

It has been suggested that higher AC/A ratios are found in myopes because recent or low myopes generally do not wear corrective lenses at near. Because they would experience a lower accommodative demand but an equivalent vergence demand than emmetropes during a near vision task, this could cause an upregulation of their AC/A ratio. This hypothesis was tested in a study of new myopes with a pattern of constant spectacle wear [38]. Their AC/A ratios were still higher than those of long-term myopes and emmetropes.

Accommodation

In both closed-loop and open-loop accommodative stimulus conditions, lower accommodative levels and inward (more myopic) post-task accommodative shifts with longer decay constants have been associated with myopia, as described below.

Closed-loop accommodation. For closed-loop conditions (visual cues present), the lower accommodative response in myopes is shown for higher stimulus levels [39-41], for myopia of more recent onset [39, 41, 42], and, most dramatically, for blur driven accommodation induced by negative lenses [40, 43, 44]. Lower blur driven accommodative responses are also associated with myopic progression [43, 44]. As modeled quantitatively by Flitcroft [45], the interaction of accommodative lag, the closeness of the targets, and the time spent in near viewing could be important factors in determining whether an eye becomes myopic.

Closed-loop accommodative hysteresis. Near work tasks can cause an inward shift of the eye's farpoint. In this situation, accommodation is presumably shifted inward causing a transient myopic refractive error, despite the presence of blur feedback in this closed loop measurement condition [46]. The magnitude of the shift has been shown to range from 0.12 to 1.3D, with a mean shift of 0.4D [47]. The decay rate is dependent on task duration, ranging from less than a minute for 10 to 20 minute tasks [48, 49] to greater than an hour for 2 hour tasks [50].

If prolonged retinal defocus is a causative factor for axial elongation and myopia, then transient myopia with a long decay constant could prolong the blur that myopes already experience during near tasks. One study comparing young adults with different refractive errors found that early-onset and recent-onset myopes had a much greater frequency of transient myopia than emmetropes or hyperopes (85%, 90%, 33% and 11%, respectively) and longer decay rates [51]. Myopic children are also more susceptible to near work induced transient myopia than emmetropic children. Transient myopia in children occurring after a ten minute task had not decayed to zero within the two minute post task measurement period [52]. More research on refractive error differences in degree and duration of transient myopia is needed.

Open-Loop Accommodation. In the absence of visual cues, accommodation stabilizes at a resting position known as tonic accommodation (TA). Lower tonic accommodation has been associated with myopia in children [53, 54] and with myopia of recent onset in adults [37, 38, 55, 56].

Open-Loop Accommodative Hysteresis. Inward or myopic shifts in tonic accommodation have been shown to occur after a sustained near viewing task [37, 54, 57, 58]. These shifts are greater in magnitude in myopes of recent onset than in emmetropes [37, 54]. In the Gwiazda study of children and young teens, this effect was inversely correlated with numbers of years myopic, so that the greatest shifts in TA were in more recent myopes, a group that typically has greater rates of progression [54].

The decay rate, or time it takes for tonic accommodation to return to its initial resting level upon cessation of a near work task, is longer in recent onset myopes than in emmetropes [51, 56, 58, 59]. These differences were enhanced for higher accommodative stimulus task levels [56] and for task duration. After a 3 minute viewing task, TA in recent onset myopes returned to base level within 90 seconds [59], but after a 15 minute viewing task, there was no evidence of decay [58].

The higher hysteresis effects in recent onset myopes may be a function of their lower initial tonic accommodation level [54, 57, 58]. Ebenholtz [57] showed a linear inverse relationship between initial accommodative resting level and accommodative adaptation in a group of emmetropes. The same inverse relationship was found across refractive error groups [54, 58]. One reason this may occur is because accommodative resting states closer to the accommodative demand of the near vision task would require less accommodative innervation than more distal tonic accommodation levels. Once the stimulus is removed, aftereffects of the accommodative response would dissipate more rapidly. Therefore, myopes, with their characteristic distal resting levels, would incur greater hysteresis effects. However, in a study in which the near task was specified to be 3.0D inward from each subject's unique resting level, recent onset myopes still showed slower regression rates than emmetropes [59].

Night time room illumination

An investigation [60] of the association between myopia in children and their night-time light exposure in the first two years was motivated by reports linking continuous light rearing in animals to abnormal eye growth, usually resulting in hyperopia and astigmatism. Surprisingly, in children there was a strong association between early night-time light exposure and later development of myopia [60]. However, two recent independent studies [61, 62] failed to find an association between light exposure during sleep and consequent development of myopia. The prevalence of myopia in children who slept with night-lights was the same as that for children who slept in the dark.

A limitation of the original study was the lack of information about the refractive status of the parents. This information was available in the follow-up studies, which reported that myopic parents used ambient lighting at night significantly more than non-myopic parents. This could be related to their poor visual acuity necessitating lighting in order to increase visibility of the child at night. It was also confirmed that myopia in children is associated with parental myopia, as has been reported previously [13, 16].

One possible explanation for the discrepant results is differences in the study samples. The more recent studies included children representative of the general population, with later onset and smaller amounts of myopia than in the Quinn et al clinical sample [60].

Sensory, Neural and Optical Factors in Myopia

We have already described some of the possible oculomotor and anatomical reasons for the accommodative anomalies associated with myopia. Another possibility may be that the optical quality of the retinal image is reduced in myopia, making it more difficult for myopes to detect and thus respond appropriately to blur.

Blur Sensitivity

Myopes are reported to have a significantly higher blur threshold than emmetropes, as well as a significantly greater within group variance [63]. In this study, subjects were cyclopleged and corrected for the viewing distance of a bipartite target. They were required to report when there

was a discernible decrease in clarity for the moving half of the target compared to the fixed half. For each refractive group, the blur threshold was equal when the target was moved in either direction, proximally or distally. This gives confidence that subjects were effectively cyclopleged and corrected properly. It also demonstrates that blur sensitivity is equal to different signed defocus. Of course, this does not preclude the possibility that the accommodative controller or the emmetropization system has an unequal gain for different signed blur as suggested by human accommodation [40, 43] and animal emmetropization studies [64].

Contrast Sensitivity

Is the reduced sensitivity to blur a result of reduced visual resolution? The contrast sensitivity function (CSF) is a useful tool to detect subtle changes in the resolution abilities of the visual system. Comparative CSF studies have been limited to moderately high myopes (greater than 6D) versus emmetropes [65-67] and to moderate versus high myopes [68]. The results have been complicated by the correction mode worn by the myopes. According to Knapp's law, when axial myopes are corrected with spectacle lenses, the image will be minified. Conversely, contact lenses (CL) will cause relative magnification. However, after taking the effects of correction into account, the results remain equivocal. When minification effects of spectacles were eliminated by having the same subjects wear contact lenses, higher myopes remained significantly less sensitive than lower myopes at the highest spatial frequency measured (24cpd) [68]. Because of CL magnification effects, the opposite result would be predicted if both myopic groups had equal CSF. In another study, when the data were mathematically transformed to account for spectacle minification, this eliminated the significant contrast sensitivity loss at the highest spatial frequency tested (23cpd) for myopes compared to emmetropes [66].

It is possible that if subjects were tested at higher spatial frequencies, closer to the CSF cutoff, where retinal and optical factors may affect the function more dramatically, clearer differences may have been measured. One study, which measured high contrast visual acuity as a function of myopic refractive error, showed that for every diopter increase in myopia there was an average reduction of one letter in log MAR visual acuity [69]. When lens-induced size effects and measurement variance are taken into account, the authors report that a reduction in VA would be confidently predicted in myopia greater than 4D in spectacle corrected myopes and 8D in CL corrected myopes. While these decrements in acuity are small, it should be noted that the accommodative controller responds to changes in blur which are smaller than what is perceptible to the viewer [70]. Thus it is possible that these small differences in reduced resolution could represent relatively large error signal differences in the sensory part of the accommodative controller.

Aberrations

In the emmetropic eye, visual resolution closely matches the neural cut-off spatial frequency or Nyquist limit of the eye, which is calculated from the sampling density of the retina (the center to center spacing of the photoreceptors). Thus, improved optics in the emmetropic eye would have little, if any, effect on visual resolution. In contrast, the resolution limits of the myopic eye may be influenced by both neural and optical factors [69]. Eye shape changes which occur in myopia development could increase receptor spacing and reduce the Nyquist limit. The eye shape changes could also modify individual ocular components (structural changes in the lens and cornea), and their relationships to each other (misalignment of their optical axes), to induce optical aberrations. These changes could set up a cycle of blur induced eye growth both indirectly, by decreased neural sensitivity and a decreased blur response, and directly by increased retinal blur.

Optical aberrations may precede and contribute to myopia development. The optical aberration we are most familiar with, astigmatism (a second order aberration), has been implicated in disrupting spherical emmetropization [71] and in contributing to myopia development [13, 72]. Recently, higher order ocular aberrations have been measured and described [73, 74]. Limited data from adults show an association of higher order aberrations and myopia [75]. In another study which used the aberroscope grid photographic technique, more than half of the 36 myopes had such high levels of aberrations that distortion of the measurement grid precluded accurate analysis. In contrast, only 2 of 16 emmetropes had poor quality photographs [76]. We are currently investigating refractive error differences in high order aberrations in this laboratory. Using a fast psychophysical ray-tracing technique where measurement is not limited by the presence of high levels of aberrations, we have shown that the prevalence of higher order aberrations is greater in both myopic children and adults compared to emmetropes [77].

Ocular Components

Infant eyes show a wide range of refractive errors because of a mismatch between the axial length and the focal plane. In the early years the eye shows coordinated growth between the axial and optical components, such that by 5 years of age most eyes are emmetropic. Then at school age, with the onset of increased near work demands, the axial length becomes longer than the focal plane in many eyes, such that distant objects are focused in front of the retina, hence myopic.

Vitreous chamber

It is well established that experimental myopia from visual manipulations in animals is related to axial elongation, especially of the vitreous chamber (for a review, see Norton, [4]). It is becoming increasingly clear that the structural basis for most human myopia, including that developing after childhood, is also elongation of the vitreous chamber [28, 78]. Interestingly, the eyes of emmetropic children with two myopic parents are longer than those of children with non-myopic parents [79].

Cornea

The cornea, as the primary refractive element in the eye, is a major source of aberrations. Corneal astigmatism degrades image quality, and could contribute an error signal to disrupt emmetropization of spherical power. It has been suggested that uncorrected astigmatism early in life could influence the development of myopia [80]. It is known that astigmatism is more prevalent in infants and young children than in adults [81-83], and the early astigmatism is corneal in origin [84]. In addition, astigmatism in the early years is associated with the onset of myopia and increased astigmatism in school-age children [13,72].

Lens

While the cornea is the major source of astigmatism in infants, in older children and adults the lens may be a source of astigmatism, especially that occurring in conjunction with myopia. Recent research on ocular components in juvenile eyes shows that the crystalline lens thins between 6 and 10 years of age, and is thinner in myopic eyes [85-87]. It has been suggested that the tension on the lens as it reaches its stretching limit induces a pseudo-cycloplegia in the myopic eye, resulting in the underaccommodation and high AC/A ratios found in young myopes, as discussed above [35]. Related to this is the suggestion that spherically asymmetric forces in the tightened ciliary muscle could induce astigmatism associated with the development of myopia [72].

Clinical Studies

With increased understanding of the mechanisms underlying the development of myopia, it is hoped that methods may be found to slow the progression of myopia, and ultimately, to retard its development in at-risk individuals. Current methods for slowing progression include spectacles, contact lenses, and drug therapy, as summarized below. Discussion of refractive surgery to render an eye less myopic is beyond the scope of this article.

Spectacle interventions

Numerous studies investigating spectacle interventions for slowing myopic progression can be found in the literature, and many have reported a benefit of bifocal lenses (for a review, see [88]). However, most of the early reports lacked adequate controls, such as random assignment to treatment groups and masked examiners, making it difficult to interpret the results. More recent investigations have been better controlled and include measures of ocular components to complement refractive error measures.

Three prospective studies with adequate controls failed to find a benefit of bifocals in slowing myopic progression in children [78, 89, 90]. More recently, the possibility that a spectacle intervention can slow myopic progression in children is provided in two studies [91, 92].

In a study by Fulk and Cyert [91], half of 82 children with nearpoint esophoria were fit with single vision lenses and the other half with bifocals with a +1.50 add. Refraction and axial length were measured every six months for 30 months. For all children, myopia progressed less over the summer than during the school year, supporting the connection between myopia and near work. In addition, there was less myopic progression in children wearing bifocals, 0.99D, compared to 1.24D for those wearing single vision lenses. However, the size of the effect was not sufficient for the authors to recommend the use of bifocals for myopic children with nearpoint esophoria.

In the Leung and Brown study [92], 68 children were randomly assigned to wear either single vision lenses, progressive addition lenses (PAL's) with a +1.50 addition, or PAL's with a +2.00 addition. Measurement of refraction and axial length was made over a two-year period. At the end of that time progression was found to be significantly slower in the groups wearing PAL's. Furthermore, there was a dose-response effect, such that the children with the higher add power had less progression after two years.

Contact lenses

Recent studies have investigated whether contact lenses, either soft or rigid gas permeable (RGP's), slow the progression of myopia in children compared to conventional single vision spectacle lenses, which are most often prescribed for myopia. Horner et al. [93] found no difference in the progression of myopia in 175 children aged 11 to 14 years, half of whom were randomly assigned to wear soft contact lenses, and the other half single vision lenses. Progression data were analyzed for 130 subjects who remained in the study after three years. Mean progression based on spherical equivalent was 1.07D for the contact lens wearers and 0.91D for spectacle wearers, which was not a significant difference. However, there was a significant increase in astigmatism in the spectacle group (-0.22D) compared to the contact lens group (-0.03D), raising the possibility that certain aberrations, which may have influenced ocular growth, may have been corrected with contact lenses but not with spectacles.

The first study of the effects of RGP lenses on myopia progression was conducted by Grosvenor et al. [94]. Mean progression of myopia after two years of contact lens wear was -0.28D, while for the spectacle wearers it was -0.80D. However, the control data were obtained retrospectively.

A recently completed study in Singapore reported that annual progression in the contact lens group was -0.42D, compared to -0.78D for the spectacle wearers [95]. Both of these studies suggest that corneal flattening accounts for some of the observed effect. Both also had a high drop out rate, especially among the contact lens wearers. In order to overcome some of the problems associated with these studies, a new prospective study [96] has incorporated design features which should help to reduce losses to follow-up and help to establish the mechanisms responsible for slowed progression of myopia with RGP contact lenses.

Drugs

One of the classic studies using drug therapy for slowing the progression of myopia concluded that the cycloplegic agent, atropine, was effective for that purpose [97]. In the thirty years since publication of this study, there have been many other attempts to use atropine and other cycloplegic drugs in an attempt to halt or slow myopic progression. Many of the recent studies investigating drug therapy for myopia have been performed in Asia, where the prevalence of myopia is much higher than in the United States [98-100].

While evidence is accumulating that atropine treatment slows myopic progression [98-100], the daily instillation of drops also has some side effects for every patient and potentially serious side effects for a few. Light sensitivity is a major complaint. Difficulty with near work activities with paralyzed accommodation is often cited. Long-term treatment with atropine can cause accommodation to take years to recover after drug treatment is stopped [101]. Lower doses may reduce the severity of side effects, but they also may be less effective. A recent study suggests that treatment with 0.5% atropine was more effective than lower concentrations (0.25% and 0.10%) in slowing progression, and that the side effects were not as severe as with higher concentrations (1.0%) [100]. Caution is advised when considering this therapy for slowing myopic progression.

Summary

As discussed in this chapter, eye growth eventuating in myopia is determined by both inherited and environmental factors. Factors identified at this time include familial myopia, myopic or emmetropic refractions in the pre-school years, and the combination of oculomotor parameters, described above, in conjunction with near work activities. The converging lines of evidence elucidating mechanisms of myopization are helping to guide clinical investigations of potential methods for control and prevention. When the next chapter on myopia is written, results emerging from these investigations may be the focal point of the discussion.

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