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Research article

What is a typical optic nerve head?

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A B S T R A C T

Whereas it is known that elevated intraocular pressure (IOP) increases the risk of glaucoma, it is not known why optic nerve heads (ONHs) vary so much in sensitivity to IOP and how this sensitivity depends on the characteristics of the ONH such as tissue mechanical properties and geometry. It is often assumed that ONHs with uncommon or atypical sensitivity to IOP, high sensitivity in normal tension glaucoma or high robustness in ocular hypertension, also have atypical ONH characteristics. Here we address two specific questions quantitatively: Do atypical ONH characteristics necessarily lead to atypical biomechanical responses to elevated IOP? And, do typical biomechanical responses necessarily come from ONHs with typical characteristics. We generated 100,000 ONH numerical models with randomly selected values for the characteristics, all falling within literature ranges of normal ONHs. The models were solved to predict their biomechanical response to an increase in IOP. We classified ONH characteristics and biomechanical responses into typical or atypical using a percentile-based threshold, and calculated the fraction of ONHs for which the answers to the two questions were true and/or false. We then studied the effects of varying the percentile threshold. We found that when we classified the extreme 5% of individual ONH characteristics or responses as atypical, only 28% of ONHs with an atypical characteristic had an atypical response. Further, almost 29% of typical responses came from ONHs with at least one atypical characteristic. Thus, the answer to both questions is no. This answer held irrespective of the threshold for classifying typical or atypical. Our results challenge the assumption that ONHs with atypical sensitivity to IOP must have atypical characteristics. This finding suggests that the traditional approach of identifying risk factors by comparing characteristics between patient groups (e.g. ocular hypertensive vs. primary open angle glaucoma) may not be a sound strategy.

1. Introduction

Glaucoma is the second leading cause of blindness worldwide (Quigley and Broman, 2006). Elevated intraocular pressure (IOP) has been identified as the main risk factor for the development and progression of the disease (Bengtsson and Heijl, 2005). Nevertheless, there is a wide range of sensitivity to elevated IOP, whereby some people suffer glaucoma at apparently normal levels of IOP (normotensive glaucoma) and others show no signs of the disease despite having elevated IOP (ocular hypertension) (Burgoyne et al., 2005; Quigley, 2005). The origin of this range of sensitivities to IOP is still not fully elucidated (Quigley, 2005). A common notion has been that the sensitivity to IOP of a specific optic nerve head (ONH) is determined, at least in part, by its biomechanical characteristics, namely the mechanical properties and geometry of the ONH tissues (Albon et al., 1995; Grytz et al., 2012; Reis et al., 2012; Sigal and Ethier, 2009; Wu et al., 2015). From this perspective, some eyes have a specific characteristic or a combination of characteristics that render them particularly sensitive to IOP and more likely to develop glaucoma, or particularly resilient to IOP and present as ocular hypertensive. This view has fueled efforts to characterize the morphology and biomechanics of eyes with various forms of glaucoma, which are then compared with those of normal and ocular hypertensive eyes in the hope that it will be possible to identify a structural or biomechanical biomarker for the disease

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(Coudrillier et al., 2015; Jonas et al., 2013; Lee and Kim, 2015; Omodaka et al., 2015; Park et al., 2015; Pijanka et al., 2014, 2015; Roberts et al., 2010).

Underlying the studies mentioned above is the assumption that ONHs that have an uncommon or atypical sensitivity to IOP, be it high sensitivity or high robustness, also have atypical ONH characteristics. Based on our recent observations of the complex nonlinear interactions between factors influencing ONH biomechanical sensitivity to IOP (Sigal, 2009, 2011; Sigal et al., 2011, 2012), we suspect that this assumption might not hold true.

In this study, we used a large set of models representing ONHs with a wide range of characteristics spanning anatomy/geometry and tissue mechanical properties to address two specific questions: (1) Do atypical ONH characteristics, necessarily lead to atypical biomechanical responses to IOP? And (2) Do typical biomechanical responses to IOP necessarily come from typical ONH characteristics? (Fig. 1) We defined typical to mean a characteristic or response with a value close to the median of the population of ONHs, and atypical for a value that is distant to the median. We studied how the threshold used to define typical vs. atypical affected the answer to the questions. A negative answer would indicate that simply splitting ONHs into typical or atypical based on their characteristics or responses is not a good approach for determining susceptibility to glaucoma.

2. Methods

2.1. Population of simulated ONHs

In order to have a well-controlled and large population of ONHs that would provide statistically robust results, we used a population of 100,000 ONH models from a previously published study (Sigal et al., 2012). The ranges and distributions for the characteristics corresponded to normal subjects and were based on the literature (Table 1) (Sigal et al., 2004, 2005). Note that atypical characteristics were still within the normal ranges. The ONH models were generated using Gaussian distributions of 8 characteristics of interest which had been identified as contributing to more than 96% of the variation in IOP-induced ONH displacements, deformations and forces among 21 characteristics (Sigal, 2009). The geometric characteristics that were varied were the radius of the eye, the thickness of the sclera, the radius of the lamina cribrosa (LC) and the anterior-posterior position of the central LC. The mechanical properties of the ONHs that were varied were the elastic modulus of the LC, the elastic modulus of the sclera, the elastic modulus of the neural tissue, and the Poisson's ratio of the neural tissue. The Poisson's ratio defines the compressibility of the tissue and was intended to account for the potential for fluid displacements, including axoplasmic flow. It should be noted that we use the term mechanical properties solely to refer to the intrinsic material mechanical properties and not the structural or geometric properties.

As before, the mechanical response of a given ONH model to an IOP elevation of 10 mmHg was calculated using a published surrogate cubic polynomial model derived from our earlier finite element models of the ONH (Sigal et al., 2012). In this study we analyzed four components of the mechanical response (Table 2): the maximum tensile strain within the LC (the 95th percentile maximum principal strain) (Sigal et al., 2005), scleral canal expansion (SCE), lamina cribrosa displacement (LCD), and the laminar median von Mises stress (a non-directional measure of the force per unit area in the LC) (Sigal et al., 2005).

2.2. Definition of typical

As a first approach we classified characteristics and responses as typical or atypical using a binary definition based on a hard percentile threshold. Specifically, we defined a typical

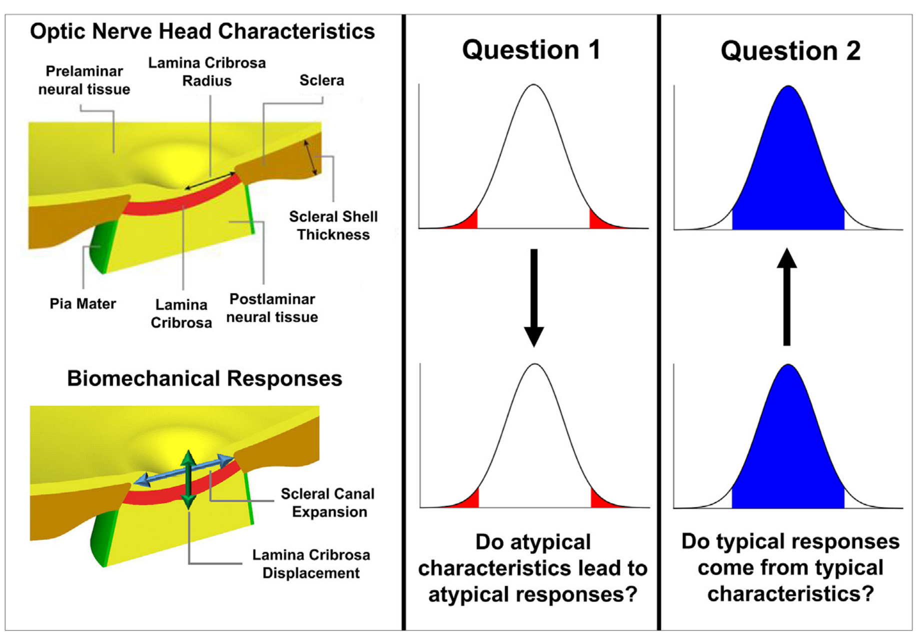

Fig. 1. Schematic of the research questions. We produced 100,000 different ONH models with random but carefully selected characteristics according to the normal distributions in Table 1. Example geometric parameters are shown on the top left panel. We simulated the response of each ONH model to a 10 mmHg increase in IOP. Four aspects of these responses were obtained for each ONH (Table 2). These included the anterior-posterior lamina displacement and the scleral canal expansion (bottom left panel). Characteristics and response values were classified as typical or atypical. Using the ONH population and their responses we addressed quantitatively two research questions (middle and rightmost columns): (1) Do atypical ONHs (those with all atypical characteristics) necessarily lead to atypical responses to IOP? (2) Do typical biomechanical responses necessarily come from typical ONH characteristics? The graphs represent the distributions of characteristics (top) or responses (bottom), classified into typical (blue) or atypical (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)