PERSPECTIVE

The Genetic Influence on Corticosteroid-Induced Ocular Hypertension: A Field Positioned for Discovery

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• **PURPOSE: To provide evidence that corticosteroid-induced ocular hypertension has a genetic component.**
• **DESIGN: Evidence-based perspective.**
• **METHODS: We conducted a comprehensive literature search for studies exploring genetic influences on intraocular pressure responses to corticosteroid treatment.**
• **RESULTS: Studies demonstrating increased risk of corticosteroid-induced ocular hypertension among first-degree relatives of affected individuals support a genetic contribution to the disease. Family and personal history of primary open-angle glaucoma also increases the risk of corticosteroid-induced intraocular pressure elevation, suggesting common genetic etiologies. A number of studies have attempted to identify predisposing genetic factors; however, reproducible findings have not yet been reported. The recent availability of large data sets with clinical and genetic data for patients affected by corticosteroid-induced ocular hypertension and glaucoma provides new opportunities to study the genetic underpinnings of this important condition.**
• **CONCLUSIONS: There is substantial evidence suggesting a genetic component to corticosteroid-related ocular hypertension and glaucoma, but specific genetic risk factors have yet to be identified. The current confluence of large genetic data sets and affordable genetic sequencing technologies has great potential for discovering the genes that increase risk for this blinding complication of corticosteroid therapy. (Am J Ophthalmol 2019;202:1–5. © 2019 Elsevier Inc. All rights reserved.)**

CORTICOSTEROIDS HAVE STRONG ANTI-inflammatory effects and are administered in ophthalmology to treat a variety of conditions, including postoperative inflammation, uveitis, and retinal vascular disorders. Unfortunately, corticosteroids can also cause an elevation in intraocular pressure (IOP) in a significant percentage of patients. This, in turn, can lead to corticosteroid-induced glaucoma, a form of open-angle glaucoma, and permanent vision loss.[1]

Recently, intravitreal corticosteroids have been preferentially used to treat various uveitic and vitreoretinal diseases, causing an increased incidence of corticosteroid-induced ocular hypertension and glaucoma.[2] An estimated one third of the population falls into the category of moderate corticosteroid responders, those who develop an IOP rise of 6-15 mm Hg from their baseline IOP. Approximately 4%-6% of the population are considered high corticosteroid responders and experience an IOP increase of at least 15 mm Hg or an IOP of over 31 mm Hg after exposure to corticosteroids.[3,4]

Potential risk factors for corticosteroid-induced ocular hypertension have been explored. Older patients and children have been identified to be at higher risk[2,4]; however, age only partially explains the variance in corticosteroid-induced IOP response. Other factors that may lead to a higher incidence of steroid responsiveness include connective-tissue disease,[5] type 1 diabetes mellitus,[5,6] and high myopia.[7]

Genetic predisposition to corticosteroid-induced ocular hypertension has been hypothesized for 6 decades,[8–10] but there has been limited progress in identifying the implicated genetic variants. Our perspective is that the risk of increased IOP secondary to corticosteroids is influenced by genetic risk factors and that recent advances in genetic sequencing and analysis, coupled with new knowledge of the genetic underpinnings of primary open-angle glaucoma (POAG) and IOP,[11] provides novel opportunities to elucidate the genetic basis of corticosteroid-induced ocular hypertension.

EVIDENCE OF GENETIC INVOLVEMENT FROM FAMILY STUDIES

STUDIES OF FAMILIES WITH MULTIPLE MEMBERS AFFECTED BY corticosteroid-induced ocular hypertension and glaucoma

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provided the first evidence for the involvement of genetics in corticosteroid response.[8,12] Investigations beginning in the 1960s found that first-degree relatives of high steroid responders had a greater likelihood of being high steroid responders themselves, with 13% of parents of high steroid responders also exhibiting a steroid response, compared to 0% of parents of low responders.[8] In this study, high responders were classified as subjects experiencing an IOP rise of 16 mm Hg or more, whereas low responders were those with 5 mm Hg or less. Among the offspring of low-corticosteroid responders, 98% were also low responders and 0% showed a high corticosteroid response.[8]

Initially corticosteroid-induced ocular hypertension was investigated as a monogenic, or Mendelian, trait where a single gene is necessary and sufficient to cause disease.[8–10,13] However, twin studies identified a heritability index of 0.35, a value consistent with polygenic or complex inheritance.[12]

CORTICOSTEROID-INDUCED OCULAR HYPERTENSION AND FAMILY HISTORY OR PERSONAL RISK OF PRIMARY OPEN-ANGLE GLAUCOMA

POAG IS ALSO A POLYGENIC TRAIT, AND RECENT GENOME-wide association studies have identified a number of POAG risk loci and also loci associated with IOP.[11,14–16] A personal and/or family history of POAG has been shown to be a risk factor for corticosteroid-induced ocular hypertension.[2,4,17] After exposure to corticosteroids, up to 90% of POAG patients can develop elevated IOP.[4,13,17] Furthermore, studies have suggested that a steroid response increases the chances that a patient develops POAG even after discontinuation of corticosteroids. For instance, 13% (36/276) of patients classified as high steroid responders (IOP $>$ 31 mm Hg during dexamethasone administration) developed POAG during a follow-up period of at least 5 years, compared to 0 of 251 low responders (IOP $<$ 20 mm Hg during dexamethasone administration).[18] A smaller study following patients with a betamethasone phosphate response found that 54% (7/13) of ocular hypertensive patients (IOP $>$ 21 mm Hg during steroid treatment) developed POAG during a follow-up period of at least 10 years, compared to 9% (2/22) of normotensive patients (IOP $<$ 22 mm Hg during steroid treatment).[19]

Close relatives of POAG subjects often have increased IOP after corticosteroid exposure compared to those who have no primary relatives with POAG.[9,10,20,21] One study found that a regimen of topical betamethasone for 6 weeks resulted in 39 of 50 (74%) POAG patients' siblings having an IOP elevation to 20 mm Hg or above, compared to only 30% of 100 selected volunteers with no known family history of POAG.[10] A similar study analyzed 75 offspring of POAG patients; the offspring received 3-6 weeks of topical betamethasone treatment and 87% had applanation pressures of at least 21 mm Hg, compared to 28% of controls without affected family members.[9] In a third study, Bartlett and associates found that 92% of first-degree offspring of glaucoma patients had an IOP increase of at least 5 mm Hg after administration of topical 1.0% prednisolone phosphate for 6 weeks.[20] In a large, population-based study, inhaled corticosteroid use was associated with a higher risk of open-angle glaucoma or increased IOP, but only in subjects with first-degree family members with a history of glaucoma.[21]

A number of studies suggest that corticosteroid-induced ocular hypertensive patients are at greater risk for developing optic nerve damage even after the steroids have been withdrawn and the pressure returns to normal. One prospective study followed 35 patients for at least 10 years after an initial treatment of 0.1% betamethasone phosphate in each eye for 4 weeks. These subjects had no recorded field defects when their IOP returned to baseline immediately after corticosteroid testing. Subjects were monitored every 3-6 months at follow-up glaucoma service examinations that included tonometry, perimetry, funduscopy, and gonioscopy. The study found that approximately 25% of subjects categorized as normotensive at study enrollment who demonstrated a corticosteroid response developed ocular hypertension during the observation period.[19] In another study of 788 patients who had been administered 0.1% dexamethasone for 6 weeks, 176 of 276 (63.8%) high responders—characterized by an IOP greater than 31 mm Hg—developed ocular hypertension during the poststudy follow-up period of 5 years or more.[18] Meanwhile, none of the 251 low responders—characterized by an IOP less than 20 mm Hg—developed ocular hypertension. These results suggest a correlation between corticosteroid response and risk for developing glaucoma over time.[18]

Overall, the relationship between corticosteroid-induced ocular hypertension and risk of POAG, particularly in families, supports the hypothesis that genetic risk factors can influence corticosteroid-related IOP elevation, and that current loci associated with POAG and IOP may also contribute to corticosteroid-induced ocular hypertension. Further exploration of this hypothesis could reveal novel genetic loci associated with corticosteroid-induced ocular hypertension and could also provide new insights into POAG pathogenesis.

GENE EXPRESSION AND PROTEIN EXPRESSION STUDIES

CORTICOSTEROID EFFECTS ON GENE EXPRESSION HAVE BEEN investigated as one approach to understand the role of steroids in IOP elevation.[22–24] Corticosteroids are known to have wide-ranging effects on gene expression and thus are likely to alter the expression of many genes that are unrelated to ocular hypertension. Discerning which altered genes are truly implicated in corticosteroid-induced ocular hypertension from those that are altered but unrelated to this phenomenon is the greatest challenge in such studies. One way to help make this distinction is to identify gene expression changes specific to the cell types related to the disease. In one study, increased expression of 503 genes was detected in cultured human trabecular meshwork cell lines derived from donors with no history of glaucoma after exposure to 10^{-7} M dexamethasone for 10 days.[24] The largest increase in expression was observed for MYOC (myocilin), a gene known to cause early-onset open-angle glaucoma.[25,26] The change in *MYOC* expression appeared to be specific for human trabecular meshwork cells, and was not observed in human umbilical vein endothelial cells, HeLa cells, human embryonic skeletal muscle cells, or optic nerve head astrocytes.

In a comprehensive proteomic study, trabecular meshwork cells from normal and glaucomatous patients were cultured and exposed to dexamethasone for 10 days. Levels of 718 proteins were quantified, and when results were compared to other similar previous proteomic studies,[23,24,27] only genes encoding myocilin and insulin-like growth factor binding protein 2 were found to be upregulated across all studies.[22] Overall these results suggest that *MYOC* may be involved in corticosteroid-induced ocular hypertension[28]; however, *MYOC* mutations have not been found in patients with corticosteroid-induced ocular hypertension.[29] Furthermore, 1 set of experiments in mice demonstrated that both wild-type and *MYOC*-knockout mice injected with dexamethasone experienced significantly elevated IOP. This suggests that MYOC is not necessary for an elevation of IOP to occur after dexamethasone treatment and may not play a major role in steroid-induced ocular hypertension.[30]

Other genes with significantly altered expression in trabecular meshwork cells exposed to corticosteroids are transmembrane 4 superfamily 1 (*TM4SF1*), tumor-associated antigen L6 (*TAAL6*), and angiopoietin-like factor (*CDT6*).[24]

HUMAN GENETIC STUDIES

MORE THAN 100 GENES HAVE NOW BEEN CONSISTENTLY associated with POAG and/or IOP in a series of recent landmark genome-wide association studies.[16,31,32] However, these loci have not yet been evaluated in patients with corticosteroid-induced ocular hypertension, and only a few genes associated with other forms of glaucoma have been investigated in steroid-responsive glaucoma. *MYOC* has been the most extensively studied, and a genetic association with *MYOC* variants or mutations and corticosteroid-induced ocular hypertension has not been identified.[29] Other candidate gene studies have been carried out, including analyses of the glucocorticoid receptor (*NR3C1*)[33]; however significant association with corticosteroid-induced ocular hypertension was not observed, possibly because of small sample size and reduced power.

Genome-wide association studies are a useful approach for discovery of genetic risk factors for complex traits such as corticosteroid-induced ocular hypertension. One such study evaluated a cohort of 64 subjects exposed to intravitreal triamcinolone. Corticosteroid responders were characterized as those with an increase in IOP greater than 6 mm Hg above baseline following intravitreal triamcinolone injection. One locus, near the 5′ end of the novel HLA complex group 22 (*HCG22*) gene, reached genome-wide significance ($P \leq 5 \times 10^{-8}$). The mucin gene *HCG22* is thought to be regulated by corticosteroids, although the precise mechanism of its function is currently unknown. These results suggested that *HCG22* may be a potential contributor to corticosteroid-induced intraocular hypertension.[34] However, there has been no independent replication of this study yet. *HCG22* expression has also been shown to increase after treatment of interleukin 1 and decrease after triamcinolone acetate treatment in cultures of trabecular meshwork cells, also supporting the hypothesis that *HCG22* may play a role in corticosteroid-induced ocular hypertension.[35]

FUTURE DIRECTIONS

DESPITE MULTIPLE LINES OF INVESTIGATION INDICATING A genetic component to corticosteroid-induced IOP rise, our understanding of the specific genetic variants that impact IOP response to corticosteroids and the transcriptomic changes induced by corticosteroids remains limited. There are several reasons for this gap in our knowledge. Human genetic studies have evaluated only a few candidate genes and/or been performed with a small number of patients. Also, there has been no integration of the differential expression in human cell lines with human genetic data for corticosteroid-induced ocular hypertension.

Recent technological developments and advancements in scientific knowledge now allow for more comprehensive studies. We now have a better understanding of the genetic risk factors for POAG and IOP. There are currently larger collections of patient DNA in biobanks across the world and from clinical trials as the importance of personalized and precision medicine has become more recognized. More powerful genetic sequencing techniques enable researchers to analyze more genetic variation, including rare variations, at a reasonable price. RNA sequencing is a powerful new tool that can be used to understand how gene expression is altered and determine which genes should be further explored as likely genetic determinants of corticosteroid-induced IOP. The confluence of these advances provides important opportunities to identify specific genetic factors influencing this disorder, forming a basis for genetic screening and avoidance of corticosteroids in patients at risk. In particular, if genetic variants that confer high risk for corticosteroid-induced ocular hypertension are identified, testing for these variants could be used to personalize treatment choices.

SUMMARY

GENETIC CONTRIBUTION TO CORTICOSTEROID-INDUCED ocular hypertension has been suspected for many decades, but only recently have scientific technologies and tools been advanced enough to comprehensively investigate these genetic influences. Evidence from studies performed thus far suggests that risk for corticosteroid-induced IOP elevation is influenced by genetic risk factors. Understanding the genetic component to the disease may allow physicians to tailor their treatment choices based on individual patients' genes. This, in turn, may prevent patients with a greater genetic predisposition for damaging corticosteroid-induced ocular hypertension from developing glaucoma and vision loss. Insights from genetic risk factors may also increase our understanding of the underlying mechanisms causing corticosteroid-induced glaucoma and could lead to targeted therapies for this condition.

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