Glaucoma Research in India

Although Indian ophthalmologists author many studies, the sheer volume of patients in the face of limited resources challenges most clinicians’ ability to devote much time to research.

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L.V. Prasad is a first-class international clinical and research institute. At a time when attacking the daunting problem of cataract blindness seemed insurmountable, private institutions in India such as L.V. Prasad Eye, Aravind Eye Care System, and Sankara Nethralaya all realized their strengths and abilities in clinical research. These centers are now not only world-class clinical facilities but also leaders in various fields of ophthalmic research.

Imagine desiring to answer a question about congenital glaucoma (either primary or secondary). Many ophthalmic institutions in India see at least one new patient with congenital glaucoma daily. This patient population is far larger than that of many top US centers combined. It would therefore be possible for one institution to prospectively investigate best therapies, etiology, genetics, and counseling related to congenital glaucoma. The research could even examine both the direct and indirect costs of this disease for a child’s family.

Alternatively, imagine wishing to investigate which type of IOL might work best in eyes with pseudoexfoliation and whether or not the addition of a capsular tension ring could prevent late IOL dislocations. At one of the major hospitals in India, over 30,000 phacoemulsification surgeries on eyes with exfoliation glaucoma are performed yearly. Research could be conducted that gathered genetic information and looked at homocysteine levels and also mortality. The Blue Mountains Eye Study suggests that patients with pseudoexfoliation die earlier from cardiovascular disease than people without the condition. Is this actually the case?

The opportunities for clinical and basic science research in India are endless. With international collaboration, the country’s doctors and scientists are developing improved research and biostatistical skills. Funding is a challenge, however, as is allocating the time for research. After all, how does one make time for research when the clinical needs are overwhelming?

As the late David Epstein, MD, once said to me, consider a patient population a personal laboratory. The Indian laboratories have tremendous capabilities. I am confident we will be seeing much more high-quality research from multiple Indian centers in the years to come.

—Alan L. Robin, MD, section editor

The overall focus of glaucoma research in India may be divided into three major categories: (1) investigator-initiated clinical research on the disease process and treatment modalities, (2) epidemiological studies designed to determine the prevalence of glaucoma and its risk factors, and (3) basic science to unravel the disease etiology.

According to a search on PubMed, more than 500 research articles on glaucoma were published over the past 3 decades by Indian authors in peer-reviewed journals that are indexed under Thomson Reuters’ Journal Citation Reports. This article provides a general perspective on the overall achievements in glaucoma research from India in light of existing resources and challenges. We would like to note that this is not a comprehensive review of all glaucoma research performed in the country, and therefore, some important works may be missed inadvertently.

AREAS OF RESEARCH: THE INDIAN PERSPECTIVE

Clinical Research

The majority of the research in glaucoma is built on unique observations of the patient populations at the
Indian clinics, which have provided an understanding of clinically relevant risk factors and their implications for the disease process. The recently concluded Silver Jubilee Annual Conference of the Glaucoma Society of India included a session called “Research: the Best From India.” These presentations focused on the role of corneal biomechanical properties in various forms of glaucoma, the 6-year incidence of primary angle-closure disease (PACD), malignant glaucoma, family history as a strong risk factor for PACD, and congenital glaucoma. Three of these presentations were published as peer-reviewed articles in the American Journal of Ophthalmology, and two were published in Ophthalmology, which indicates the standard of clinical research in India.

Epidemiological Studies
Large-scale epidemiological studies have provided insight into the prevalence of glaucoma in India. Most of these studies (Vellore Eye Study [VES], Andhra Pradesh Eye Disease Study [APEDS], Aravind Comprehensive Eye Survey [ACES], and the Chennai Glaucoma Study [CGS]) were conducted in the southern part of India and later in central (Central India Eye and Medical Study [CIEMS]) and eastern (West Bengal Glaucoma Study [WBGS]) India. Despite using modern techniques for diagnosing glaucoma, the prevalence of primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), and exfoliation glaucoma varied considerably, which was attributed to the definitions used to characterize these forms of the disease.

All of these major studies provided important information. POAG was shown to be more common than PACD. About 90% of POAG in the population was undetected, and both POAG and PACD were more common in urban than rural cohorts. Aging was consistently a risk factor in these studies, and changing demographics and senescence will significantly increase the burden of glaucoma in this country. Currently, there are no major tools to screen the population at large, so opportunistic screening at the clinics remains the only mode by which to detect early disease.

A recent effort at the L.V. Prasad Eye Institute was undertaken to enable the vision technician at primary levels of eye care to diagnose glaucoma. An ongoing study, Glaucoma Epidemiology and Molecular Genetics Study (GLEAMS), is trying to characterize the best combination of diagnostic tools to detect the disease in the general population.

Some of these population-based studies like the CGS and APEDS are currently engaged in a longitudinal follow-up of their cohorts; CGS has already reported on the 6-year incidence of PACD.

Basic Science Research
Research in basic science has largely focused on genomics and, lately, proteomics. The initial approaches in genomics were directed toward screening for mutations of known candidate genes in POAG (MYOC), exfoliation glaucoma (LOXL1), primary congenital glaucoma (CYP1B1), and other developmental glaummas (FOXC1, PAX6) that indicated a similar involvement as observed globally. A large proportion of other candidate genes (OPTN, NTF4, OPTC, WDR36, LTBP2) and variations observed through genome-wide association studies, however, could not be replicated in Indian patients due to the small effect sizes, changes in sample sizes, population substructuring effects, and ethnic diversity.

Some modest genetic associations were observed for the disease or quantitative traits leading to POAG (ATOH7, CDC7, CDKN2B, SIX1/SIX6, TGFBR3), PACG (ABCC5, PLEKHA7, COL11A1, and a variant between PCMTD1 and ST18), and exfoliation glaucoma (CAGNA1A). These findings need to be validated in large Indian cohorts and with functional analysis. Some studies have convincingly demonstrated the functional analysis of some mutant proteins like MYOC, OPTN/TBK1, and CYP1B1, along with genotype-phenotype correlation in glaucoma pathogenesis. The current emphasis is on discovering biomarkers for predictive testing, which would be an important contribution to the management of glaucoma.

CHALLENGES AND OPPORTUNITIES
Training
Exposure to research and training in research methodology at the residency level in the country need to improve. Based on information from the Internet, the five institutes that contribute to more than 90% of the publications from the country train only 12% of the total residents in India. The Indian Journal of Ophthalmology and the Journal of Clinical Research and Methodology conduct workshops on research methodology. Over the past 10 years and about 20 workshops, 1,400 delegates from India have been trained. It is difficult to measure the impact and effectiveness of these kinds of training programs, but they are a start.

Clinical Load and Opportunity Costs
The ratio of the number of ophthalmologists to the population makes it difficult for clinicians to find the time to conduct research. Some of the institutes allocate time for research, and this approach may need to be emulated by more centers.
Research Focus
There is a need to focus on angle-closure disease, which has a unique clinical presentation and treatment outcomes in Indian patients compared with white and East Asian populations. The “Trilab” initiative, which involves three tertiary centers in Southern India (L.V. Prasad Eye Institute, Sankara Nethralaya, and Aravind Eye Care Systems), is a joint program designed to elucidate the pathogenesis and progression of PACG from a clinical and “omics” perspective, including (and not limited to) genomics, transcriptomics, and proteomics. We believe that, with adequate funding and collaboration, India is poised to conduct well-structured, randomized, controlled trials to answer pertinent questions about angle-closure disease.

Funding
A lack of adequate extramural funding has motivated clinicians and scientists to undertake short-term projects with limited goals. Unlike in nations that offer extramural funding, intramural grants, and significant donations for research, researchers in India have always been deprived of big grants on a sustained basis. Research questions have thus often been tailored to suit the minimum resources that are available, which stymies a comprehensive approach and large-scale collaborations on a national level. The efforts by the funding agencies of the Government of India (Ministry of Science and Technology) that were initiated through a pan-Africa effort to map genetic mutations in POAG and primary congenital glaucoma to develop a DNA-based diagnostic tool are encouraging.

CONCLUSION
Glaucoma research in India has shown great potential. Concerted clinician-scientist and multicenter collaborations with adequate funding are needed to answer the unique questions faced by the glaucoma clinicians, scientist, and patient community.

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