“Perhaps the greatest way that the Pediatric Eye Disease Investigator Group (PEDIG) has impacted ophthalmology at Mayo Clinic has been through the transition to evidence-based care and its effect on our patients — particularly those with amblyopia,” says Jonathan M. Holmes, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, and immediate past PEDIG national network chair.

Dr. Holmes continues: “Prior to PEDIG, if we saw a child with combined anisometropic and strabismic amblyopia we would simultaneously start glasses (based on the cycloplegic refraction) and fairly intense patching (at least six hours a day). Now, based on the evidence from a series of amblyopia treatment trials, we start glasses first. PEDIG studies show that at least a quarter of children will have resolution of their amblyopia with such optical treatment alone.

“If the child doesn’t completely respond to glasses we try more intense patching — such as six to eight hours each day — or we change the glasses lens to plano to increase penalization while using atropine.

“Despite these treatment advances, some children are still left with residual amblyopia: Up to 50 percent have worse than 20/25 vision. We continue to investigate alternative approaches, such as oral levodopa as an adjunct to patching. We’re also planning a new amblyopia treatment trial that uses binocular game play on an iPad. This approach has shown early promise in pilot studies. By harnessing children’s enthusiasm for computer games in PEDIG multicenter randomized trials, it is possible that in a few years we will have evidence that allows us to offer treatment of amblyopia without patching or drops.”

**Clinical parameter assessment**

“Another way PEDIG has influenced our practice is through development of a more rigorous approach to assessing clinical parameters,” says Dr. Holmes. “The Mayo Clinic Department of Ophthalmology has led the development of standardized methods for clinical trials to assess visual acuity, stereo-acuity and strabismus control. It is also the first to pilot test these measures on patients. By incorporating these methods into day-to-day practice, we’ve reduced the variability of routine testing.

“The department also led the development of new instruments to assess health-related quality of life, including questionnaires for childhood intermittent exotropia, nasolacrimal duct obstruction and adult

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The Pediatric Eye Disease Investigator Group (PEDIG) is a national network of pediatric ophthalmologists and pediatric optometrists that conducts randomized clinical trials and observational studies in childhood eye disease to provide practical answers to questions that ophthalmologists face every day in the management of patients. PEDIG involves more than 200 investigators at more than 100 sites and typically runs four to seven simultaneous studies in the areas of amblyopia, strabismus and other childhood ophthalmic conditions. PEDIG is funded by the National Eye Institute of the National Institutes of Health.
Investigators first speculated that intracranial pressure (ICP) may have a role in modulating optic nerve changes associated with glaucoma nearly 90 years ago. More recent retrospective and prospective studies have confirmed an association between reduced ICP and primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG), suggesting ICP as a risk factor for glaucoma. Unfortunately, the association between ICP and glaucomatous optic neuropathies has been difficult to study in a controlled environment because of the absence of a suitable animal model.

In an article published in *PLOS ONE* in December 2013, Michael P. Fautsch, Ph.D., at Mayo Clinic’s campus in Rochester, Minnesota, and colleagues reported a novel rat model that can be used to study the role of ICP modulation on optic neuropathies. “The rat intraventricular cannula (IVC) model is the first comprehensive animal model in which ICP can be manually reduced or increased over an extended period of time to study the role of ICP in optic nerve pathology,” says Dr. Fautsch.

In a study carried out in accordance with recommendations in the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health, Dr. Fautsch and his team compared stainless steel cannulae placement in the cisterna magna or lateral ventricle in Sprague-Dawley and brown Norway rats. The cannula was attached to a pressure transducer connected to a computer that recorded real-time ICP. Based on their ability to maintain an implanted cannula for at least four weeks with minimal surgical issues, the brown Norway rat with a stainless steel cannula inserted into the lateral ventricle became the animal of choice for subsequent experiments.

To complete the model (Figure), a column filled with artificial cerebrospinal fluid (CSF) was placed so that the top level of the artificial CSF fluid was at head level of the brown Norway rat. The cannula was attached to a pressure transducer connected to a computer that recorded real-time ICP. Based on their ability to maintain an implanted cannula for at least four weeks with minimal surgical issues, the brown Norway rat with a stainless steel cannula inserted into the lateral ventricle became the animal of choice for subsequent experiments.

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To complete the model (Figure), a column filled with artificial cerebrospinal fluid (CSF) was placed so that the top level of the artificial CSF fluid was at head level of the brown Norway rat. The artificial CSF syringe column was attached in parallel with the pressure transducer. ICP at baseline and with column lowered or raised at various positions were compared using the unpaired Student t-test. Results showed:

- Average ICP at head level was 5.5±1.5 cm water.
- Positioning of the artificial CSF column by 2 or 4 cm below head level reduced ICP by 33 percent and 73 percent when compared with baseline ICP.
- Raising the column above head level by 2 or 4 cm.

**Clinical trials**

Dr. Holmes continues: “PEDIG also provides an avenue for participation in the leadership of clinical trials. Brian G. Mohney, M.D., with the Department of Ophthalmology at Mayo Clinic in Rochester, is currently the national protocol chair for the intermittent exotropia protocol comparing patching therapy with observation. Rochester research team members Sarah R. Mickow and David A. Leske serve on PEDIG protocol planning committees and steering committees. Tomohiko Yamada, O.D., of Rochester, is an investigator in several PEDIG studies. Mickow, Lindsay D. Klaehn and Laura Lepor, C.O., at Mayo Clinic in Rochester, are masked examiners for several studies.

“Our research team currently participates in two PEDIG randomized clinical trials. We welcome referrals of children who might be eligible,” says Dr. Holmes. Studies include:

- **Hyperopia Treatment Study 1 (HTS1),** to compare visual acuity outcomes and development of strabismus after three years in children ages 12 to <72 months with moderate hyperopia — spherical equivalent +3.00 diopeters (D) to +6.00D — who are prescribed glasses either immediately or later (only after confirmation of prespecified deterioration criteria).
- **Convergence Insufficiency Study (CITS),** to determine the effectiveness of home-based computer therapy for symptomatic convergence insufficiency compared with traditional home-based, near-target push-ups and placebo treatment.

“We plan to launch two new randomized clinical trials in 2014, one studying the new binocular computer game approach to treating amblyopia and one investigating the use of over-minus spectacles to treat childhood intermittent exotropia,” says Dr. Holmes.

**For more information**

Contact Rebecca A. Nielsen, study coordinator, at 507-284-5833 or nielsen.rebecca@mayo.edu, or visit www.clinicaltrials.gov.
Study to Explore the Prevalence of Angle-Closure Glaucoma and Appropriate Laser Peripheral Iridotomy in Caucasian Populations

Angle-closure glaucoma (ACG) differs from many eye diseases in that it is a preventable cause of permanent blindness if caught soon enough. ACG is also the second-leading cause of blindness in Asian populations throughout the world.

A new study focuses on the prevalence of asymptomatic angle closure in a predominantly Caucasian population and the efficacy of laser peripheral iridotomy (LPI) in treatment. “ACG has been regarded as an uncommon disease in non-Asian ethnic groups due to the low prevalence reported in large population-based research — 0.04 percent in the Beaver Dam study and 0.06 percent in the Melbourne study,” says Syril K. Dorairaj, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Jacksonville, Florida. “Based on those results, ophthalmologists have tended to underuse gonioscopy during routine eye examinations for Caucasian populations.”

In those studies, either gonioscopy was not performed or no details were reported regarding the method of diagnosis of angle status. In contrast, when 4,297 study participants from northern Italy were screened by ophthalmologists and diagnosis was obtained using methods including gonioscopy, primary angle-closure glaucoma (PACG) was reported in 0.6 percent of the patients. In a similar study of 1,636 participants in South Brazil (of whom 72 percent identified as white), prevalence of PACG was 0.7 percent.

“The high prevalence of PACG is significant, as it may be preventable if iridocorneal apposition is diagnosed and reversed early, before intraocular pressure (IOP) is elevated,” says Dr. Dorairaj. “For PACG to be prevented by early LPI, however, it is essential that darkroom gonioscopy be performed routinely and asymptomatic angle closure has to be diagnosed.”

ACG in Caucasians

It is difficult to formulate guidelines for screening unless the prevalence of asymptomatic angle closure in Caucasians is known. Dr. Dorairaj and his team will screen 5,000 volunteer Caucasian hyperopes. “A large sample is required because previous studies have shown less than 1 percent iridocorneal apposition,” says Dr. Dorairaj. “From this study, if only 50 cases are detected and only 25 participants agree to follow-up after LPI surgery, there will be enough data for examining the efficiency of LPI.”

All included subjects will undergo detailed ocular examination including:
Peripheral laser iridotomy

Dr. Dorairaj’s team will also examine the efficacy of LPI in widening appositionally closed angles in study participants via a combination of surgical and theoretical methods:

- Participants who are identified as candidates of asymptomatic angle closure will undergo LPI after the anterior segment is imaged with ultrasound biomicroscopy (UBM).
- Axial length and keratometry will be measured before and after LPI.
- Pupil dilation and constriction contributes significantly to the changes in the iris contour, so the anterior segment will be imaged over a period of time in which the patient is exposed to different light conditions (Figure). The images will be analyzed to characterize the iris contour.

The team will measure iris concavity, chord length, angle opening distance and angle recess area to develop a finite element model based on the images obtained from clinical examination and UBM images. After LPI is performed, the anterior segment will be imaged via a procedure identical to the pre-LPI screening and the images will again be evaluated.

“Our goal is to assess the efficacy of LPI in these patients and identify patient-specific LPI guidelines,” says Dr. Dorairaj. “This work will be a step toward development of diagnostic and predictive computational models of the anterior eye, to detect angle closure at its early stages and to treat it effectively.”

Test early and often

“Testing for ACG should be provided early and at every patient visit,” says Dr. Dorairaj. “Skillful use of darkroom gonioscopy and correct interpretation of its findings may help ophthalmologists to recommend prophylactic LPI only in the eyes of patients who truly need it.”

For more information
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