Two novel glial autoantibodies discovered in the past 15 years enable recognition of patient subsets with antigen-specific central nervous system inflammatory demyelinating autoimmunity manifesting as optic neuritis. Since introduction of live transfected cell-based assays, myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG) has emerged as a reproducible marker for a subset of patients with optic neuritis, aquaporin-4 immunoglobulin G (AQP4-IgG)-seronegative inflammatory central nervous system demyelinating disorders with neuromyelitis optica spectrum disorder (NMOSD)-like phenotype, and acute disseminated encephalomyelitis (predominantly in children).

Recent studies suggest the association of MOG-IgG seropositivity with recurrent optic neuritis attacks can lead to significant visual morbidity. Because there are few large studies of MOG-IgG-seropositive optic neuritis, however, the clinical phenotype is poorly defined.

To better define the clinical entity and anticipate visual outcomes, John J. Chen, M.D., Ph.D., a neuro-ophtalmologist at Mayo Clinic in Rochester, Minnesota, and a team of researchers conducted a multicenter, observational case series to determine the presenting signs and symptoms, radiologic abnormalities, accompanying neurological deficits, and visual outcomes of a large cohort of patients with MOG-IgG-seropositive optic neuritis. Study results were published in the *American Journal of Ophthalmology* in 2018.

**Characteristics and visual clues**

Researchers identified 87 patients seen at Mayo Clinic between 2001 and 2017, or elsewhere in 2016 and 2017, who had a clinically documented history of optic neuritis at any time and serum available that tested positive for MOG-IgG.

Patients were classified as having a single episode of optic neuritis, recurrent optic neuritis, chronic relapsing inflammatory optic neuropathy, neuromyelitis optica spectrum disorders-like phenotype, acute disseminated encephalomyelitis, multiple sclerosis, or “optic neuritis plus” for patients with additional neurological symptoms.

Patients’ medical records were reviewed for presence of pain, fundus appearance at onset, visual acuity at the worst optic neuritis attack nadir and at last follow-up, number of attacks, other neurological symptoms, magnetic resonance imaging (MRI) findings, and immunotherapy and outcome.

Characteristics of the cohort include:

- Females comprised 57 percent.
- Median age at onset was 31 (range 2 to 79) years.
- Median number of optic neuritis attacks was 3 (range 1 to 8), median follow-up was 2.9 years (range 0.5 to 24 years), and annualized relapse rate was 0.8.
- Average visual acuity at nadir of worst attack was count fingers. Average final visual acuity was 20/30; for five patients (6 percent), average final visual acuity was less than or equal to 20/200 in either eye.
- Optic disk edema and pain each occurred in 86 percent of patients.
- MRI showed perineural enhancement in 50 percent and longitudinally extensive involvement in 80 percent.
- Twenty-six patients (30 percent) had recurrent optic neuritis without other neurological symptoms, 10 (12 percent)
had a single episode of optic neuritis, 14 (16 percent) had chronic relapsing inflammatory optic neuropathy, and 36 (41 percent) had optic neuritis with other neurological symptoms (most often neuromyelitis optica spectrum disorder-like phenotype or acute disseminated encephalomyelitis).

• Only one patient was diagnosed with multiple sclerosis; that patient had a low MOG-IgG titer.
• Persistent MOG-IgG seropositivity occurred in 61 of 62 patients (98 percent).
• A total of 61 percent received long-term immunosuppressant therapy.

“Our team identified five major findings in our review of visual outcomes and characteristics in this cohort,” says Dr. Chen. Those findings are as follows:

• The inflammatory course is diverse; in most cases optic neuritis is recurrent, with or without additional neurological features.
• Despite recurrence of attacks, most patients retain functional vision.
• Optic disk edema and bilateral disease are common.
• MRI evidence of optic nerve sheath and periorbital tissue involvement is common in the acute attack.
• MOG-IgG-positive neuroinflammation is a distinct entity from multiple sclerosis and AQP4-IgG-seropositive NMOSD.

“Our study indicates that MOG-IgG seropositivity predicts a relapsing inflammatory disease process with recurrent optic neuritis as a common feature. MOG-IgG positivity should be suspected if optic disk edema is moderate to severe at onset or if MRI shows optic nerve sheath involvement,” says Dr. Chen. “Despite optic neuritis attacks being severe and recurrent, however, most patients retain good functional vision. It remains to be determined whether MOG-IgG serostatus in the remission phase of optic neuritis will predict future attacks.”

For more information

PedEyeQ Assesses Quality of Life in Children With Eye Conditions

“Patient-reported outcome measures are increasingly recognized as important for assessing an individual’s health and well-being,” says Jonathan M. Holmes, M.D., with Ophthalmology at Mayo Clinic in Rochester, Minnesota. “In pediatric eye care, there are several vision-related survey instruments designed for specific eye conditions, but none that can be used across the spectrum of eye disease.”

Since 2014, Dr. Holmes’ research team at Mayo Clinic, in collaboration with Eileen E. Birch, Ph.D., and her team at Retina Foundation of the Southwest, Dallas, has been working to develop patient-reported outcome measures that reflect concerns about eye-related quality of life and functional vision. Initial results were published in Journal of AAPOS in 2016, 2017 and 2018. The complete Pediatric Eye Questionnaire (PedEyeQ) was published in American Journal of Ophthalmology in January 2019.

Stage 1: Research identifies concerns
Researchers initially enrolled 328 children. They interviewed children age 5 years and older (180 children) and all 328 parents to identify specific concerns. These children represented the range of eye conditions across 10 diagnostic categories: amblyopia, anterior segment, central nervous system-related vision loss, esotropia, exotropia, hypertropia, nystagmus, orbital condition, refractive error, and retina and optic nerve. The aim was to recruit 10 patients in each of three age groups (0 to 4 years, 5 to 11 years, 12 to 17 years), including racial or ethnic minorities.

The researchers reviewed transcribed interviews and coded specific eye-related quality-of-life and functional vision concerns, which they then reviewed to formulate questions to address specific child and parent concerns. The result was 614 individual child questions and 589 parent questions.

Stage 2: Developing the PedEyeQ
Stage 2 focused on development of a master questionnaire. Researchers aimed to identify no more than 100 questions for further refinement. The original questions were eliminated if they were similar to another question, confusing or unclear, or if the content was too narrow or had limited applicability across socioeconomic and cultural groups.

In 2017-2018, researchers enrolled a new cohort of 444 children (0 to 17 years old) across the 10 diagnostic categories to evaluate the master questionnaire. All parents and 277 children ages 5 to 17 years completed this master questionnaire. The final PedEyeQ was developed from analyses of responses on the master questionnaire; factor analysis defined specific unidimensional domains, and Rasch
analysis established performance, calibration and scoring.

The researchers formatted questions to create three different questionnaires: child (for completion by the child), proxy (paralleling the child questionnaire but from the parent’s perspective) and parent (the parent’s own experience).

Child 5- to 11-year-old PedEyeQ: 40 total questions over four domains (functional vision, bothered by eyes or vision, social, and frustration or worry).

Child 12- to 17-year-old PedEyeQ: 39 total questions over four domains (functional vision, bothered by eyes or vision, social, and frustration or worry).

Proxy 0- to 4-year-old PedEyeQ: 29 total questions over three domains (functional vision, bothered by eyes or vision, and social).

Proxy 5- to 11-year-old PedEyeQ: 39 total questions over five domains (functional vision, bothered by eyes or vision, social, frustration or worry, and eye care).

Proxy 12- to 17-year-old PedEyeQ: 42 total questions over five domains (functional vision, bothered by eyes or vision, social, frustration or worry, and eye care).

Parent PedEyeQ: 35 total questions over four domains (impact on parent or family, worry regarding child’s eye condition, worry regarding child’s self-perception and interactions, and worry regarding child’s visual function).

“By following a rigorous process, we have generated comprehensive questionnaires that can be used to assess the two broad areas of eye-related quality of life and functional vision in children of any age with any eye condition,” says Dr. Holmes. “Our subsequent third stage of this research will evaluate construct validity, reliability and responsiveness of the derived questionnaires in a new patient population.

“In March 2019, we reported at the American Association for Pediatric Ophthalmology and Strabismus annual meeting that children with bilateral visual impairment have markedly reduced functional vision and eye-related quality-of-life scores, which was the first step in validating this new PedEyeQ instrument.”

The new questionnaires are freely available on the Pediatric Eye Disease Investigator Group website.

For more information


Pediatric Eye Disease Investigator Group. www.pedig.net.

Biopsy Recommended for Patients With Clinical Characteristics of IgG4-ROD

Immunoglobulin G4-related ophthalmic disease (IgG4-ROD) is a fibroinflammatory condition characterized by a dense lymphoplasmacytic infiltrate with a preponderance of IgG4+ plasma cells and fibrosis, which was first noted in the pancreas. IgG4 disease was later described as a syndrome, in 2003, when other organ involvement was noted in the patients with IgG4-related pancreatitis. Orbital involvement was first reported in 2007 — primarily in the form of dacryoadenitis. Subsequent reports describe involvement of the lacrimal gland, orbital soft tissue, extraocular muscles (EOMs) and orbital peripheral nerves. Primary involvement of the EOMs in IgG4-ROD, and lacrimal gland enlargement can lead to diagnostic confusion with Graves’ orbitopathy (GO), the most common inflammatory disease of the orbit.

James A. Garrity, M.D., and a research team with Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, conducted a retrospective, observational study to describe findings among patients with clinical overlap of IgG4-ROD and GO, illustrate the diagnostic challenges, and determine key features that may aid in achieving the correct diagnosis. Results were published in Ophthalmic Plastic and Reconstructive Surgery in 2018.

Diagnosis criteria
Researchers retrospectively identified patients who had diagnoses of GO and IgG4-ROD and were seen in Ophthalmology at Mayo Clinic in Rochester, Minnesota, between June 2009 and November 2013. The team reviewed health records to characterize symptoms, thyroid status, and radiologic, serologic and histologic findings that led to the diagnosis of IgG4-ROD.

Clinical data collected included patient age, sex, smoking status, medical history and thyroid-related history, as well as examination findings such as vision, pupils, motility,

James A. Garrity, M.D.
proptosis, lid retraction or lag, and other signs or symptoms of orbital inflammation. Researchers also collected laboratory values for thyrotropin receptor antibodies, total serum IgG and serum IgG4.

The diagnosis of IgG4-ROD was based on a biopsy and included the number of IgG4+ plasma cells per high-power field (HPF), and the ratio between IgG4+ and IgG+ cells identified by immunohistochemical staining. A finding of 10 or more IgG4 cells per HPF and a ratio of IgG4+-to-IgG+ cells greater than 40 percent were typical findings in the diagnosis of IgG4-ROD.

Among the eight patients (seven male and one female) included in the study:

- Mean age was 46 years.
- Time between diagnoses of GO and IgG4-ROD ranged from one month to eight years.
- Imaging showed enlarged extraocular muscles in all patients.
- Enlarged infraorbital nerves were seen in four patients.
- Tissue biopsy showed CD20+ lymphocytes with a large proportion of IgG4 plasma cells in seven of eight orbital specimens.
- Six patients had a ratio of IgG4-to-IgG cells greater than 40 percent.

Treatment included rituximab in all patients. “Symptoms improved substantially in six patients after rituximab treatment, and two had progression or minimal improvement,” says Dr. Garrity. “These two patients were subsequently treated with intravenous corticosteroids and methotrexate, or mycophenolate mofetil, and had symptom resolution.”

**Patient subgroups**

“The eight patients in this study illustrate the clinical overlap of GO and IgG4-ROD, which can lead to confusion for the clinician. Although clinical, laboratory, radiologic and histologic features support each diagnosis, there are no pathognomonic laboratory or clinical findings. GO remains a clinical diagnosis, and IgG4-ROD may be misdiagnosed,” says Dr. Garrity.

Researchers separated the eight patients into three groups:

- **Patients one and two** had a past serologic diagnosis of Graves’ disease with orbitopathy (positive thyrotropin receptor antibodies), but the disease did not follow the expected clinical course for GO and they were later found to also have IgG4-ROD.
- **Patients three, four, five and six** had IgG4-ROD that was initially missed and incorrectly diagnosed as GO.
- **Patients seven and eight** had presumed GO and IgG4-ROD simultaneously.

“Some key features help distinguish the conditions,” says Dr. Garrity. “GO is likely if findings include increased thyrotropin receptor antibodies, lid retraction or lid lag, and a characteristic pattern of enlarged extraocular muscles with typical tendon-sparing morphology. Findings suggestive of IgG4-ROD include a history of asthma and progressive orbital inflammation disease in patients with a previous diagnosis of GO, a disproportionately large lateral rectus muscle, and enlarged infraorbital nerves.

“Corticosteroid dependency with noninflamed eyes is not typical of GO and should lead the clinician to consider IgG4-ROD. Histologically, GO does not show fibrosis, and chronic inflammation is minimal compared with that in IgG4-ROD. An increased serum IgG4 level and a biopsy showing greater than 10 IgG4+ plasma cells per high-power field and an IgG4-IgG ratio greater than 40 percent will support the diagnosis of IgG4-ROD.

“GO and IgG4-ROD are complicated inflammatory processes that present diagnostic challenges. We recommend biopsy for patients who do not follow the usual clinical course of GO or have clinical characteristics of IgG4-ROD.”

**For more information**