Neuro-ophthalmology

Five new things

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Summary

The field of neuro-ophthalmology is broad and interacts with other disciplines in neurology and ophthalmology along with neurosurgery, neuroradiology, rheumatology, and infectious disease. A number of interesting advances in diagnostic criteria, monitoring ability, and disease etiology have occurred in the last year that will improve our ability to take care of patients.

As a field, neuro-ophthalmology interacts with a large number of other specialties and as a result advances in any number of different fields apply to neuro-ophthalmology. The last year has produced a number of interesting advances in diagnosis, management, etiology, and treatment of a variety of different conditions seen by neuro-ophthalmologists.

Idiopathic intracranial hypertension (IIH) is a relatively commonly seen neuro-ophthalmic disorder that if left untreated can produce severe visual loss. The diagnostic criteria for adults include a CSF pressure greater than 25 cm of water along with normal CSF constituents, normal neuroimaging, and a normal examination (abducens palsy allowed). IIH in the pediatric population is also well recognized but the criteria for what constitutes elevated pressure in this population have not been well established until now. In 2 articles from Children's Hospital of Philadelphia (CHOP), standard pressures for the pediatric population and the effect of position, legs flexed or extended, on pressure were established.^{1,2} A prospective study measured CSF pressure in 197 patients age 1–18, none of whom were on medications that would influence intracranial pressure or had a medical condition that would influence intracranial pressure. A normal range of 11.5–28 cm of water was established. Moderate to deep sedation produced a slightly higher opening pressure than no sedation and a small but statistically significant effect of body mass index (BMI) on CSF pressure was noted. A post hoc analysis of 52 patients with normal BMI and no sedation showed an upper limit of 25 cm of water for opening pressure. These findings were replicated in a smaller study of 44 patients from the University of Mississippi.³ Using the same 10%–90% range of values the CHOP group used, these authors found a range of 11–32 cm of water for CSF pressure in normal controls. In a second study, the CHOP group measured opening pressure with the legs flexed and again with the legs extended.² In the flexed position the

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average pressure was 25.1 cm of water compared to 24.4 cm of water with the legs extended. The difference of 0.6 cm of water was statistically significant but is unlikely to be clinically significant. However, when looking at the individual patient results, 3 patients had 6–7 cm drops in pressure when the legs were extended. Interestingly, these 3 patients also had opening pressures greater than 20 cm of water. So, in patients with a pressure below 20 cm, extending the legs will change the pressure a small amount and be unlikely to change the clinical diagnosis. Occasionally, in a patient with an opening pressure greater than 20 cm, a more significant pressure drop will occur with extending the legs and should be done in that setting to arrive at the correct diagnosis. Prior to this series of articles pressures above 18 cm of water were thought to be abnormal in children and the effect of leg flexion vs leg extension was not known. Accurate data on the range of normal is critical when the disease definition requires having a test result out of the range of normal.

In neuro-ophthalmology, giant cell arteritis is recognized as a true emergency. Accurate diagnosis and early treatment can dramatically change the natural history outcome of bilateral blindness in one-sixth of patients and unilateral blindness in another one-sixth. One of the questions about giant cell arteritis has always been what causes this rather unique condition. Giant cell arteritis occurs after age 50 and increases in frequency with each passing decade. In addition, when untreated (published series prior to the development of prednisone) the disease would spontaneously remit in a large percent of patients. Work in progress has shown that infection with *Burkholderia*, specifically a variant of the *pseudomallei* strain, might be the inciting cause for giant cell arteritis. A study from the University of Utah has found DNA from *Burkholderia* in temporal artery biopsy specimens positive for giant cell arteritis.^{4,5} Immune testing for lipopolysaccharide from *Burkholderia* in the blood of patients with positive biopsies is also positive. In patients with negative temporal artery biopsies there is no DNA in the biopsy or antibody positivity in the blood. In addition, *Burkholderia* has been cultured from 2 temporal artery biopsies positive for giant cell arteritis. *Burkholderia* is an intracellular infection that is difficult to culture and typically is associated with sepsis and death. The strain seen in patients with giant cell arteritis is missing a Type 3 secretion that is associated with virulence. In a murine model of *Burkholderia* infection mortality is reduced with the use of prednisone only and antibiotic only, with combination treatment with prednisone and antibiotic producing the greatest reduction in mortality. While patients with giant cell arteritis do well with current treatment regimens of prednisone only there is significant morbidity with long-term prednisone in this population. In addition, there are patients who will lose vision despite starting treatment. In very preliminary work the level of lipopolysaccharide from *Burkholderia* drops with antibiotic treatment plus prednisone but does not drop with prednisone treatment only. These findings raise several interesting questions. Will antibiotic therapy reduce the duration or dose of prednisone needed to treat giant cell arteritis, thus reducing prednisone side effects? Will the risk of vision loss after starting treatment be reduced? Will a similar infectious etiology be found in other vasculitides? Finally, on a historical note, in the second article by Horton et al.⁶ describing giant cell arteritis in 1934, they postulated an infectious etiology and wondered if *Actinomyces* was the causative organism.

If giant cell arteritis is the number 1 neuro-ophthalmic emergency, then third nerve palsy from posterior communicating artery aneurysm must be number 2. In a patient with an aneurysmal third nerve palsy diagnosis and treatment before the aneurysm ruptures dramatically reduces morbidity and mortality. In a previous era conventional angiogram with attendant risk from the procedure itself was the only diagnostic option and efforts were focused on deciding who would undergo angiography, i.e., “the rule of the pupil.” In the modern era, safe, relatively noninvasive imaging is widely available and can be used to screen patients who we might have not diagnosed until after aneurysm rupture in the past. Our 2 choices for diagnostic testing are CT angiogram (CTA) and magnetic resonance angiogram (MRA). When comparing the 2 techniques the aneurysm detection rate is very similar. However, what unfortunately is not compared in studies looking at aneurysm detection rate with CTA vs MRA is the radiologist’s ability to interpret the studies obtained. In a retrospective study from Emory University the records of 17 patients with acute, isolated third nerve palsy seen at their institution were reviewed.⁷ Eight of the patients were initially seen and underwent testing at outside institutions and were then referred to Emory. In these 8 patients the outside noninvasive imaging was read as normal. In 7 of the 8 cases the outside imaging was reviewed by the authors and found to show the aneurysm. Two factors were implicated in these misdiagnosed cases. In 6 of 7 cases the radiologist was given a vague or incorrect clinical history, i.e., “headache,” or “Horner syndrome.” The second factor was the training of the radiologist. Five of the 7 radiologists were general radiologists, without formal neuroradiology training. One of the 7 radiologists had trained in neuroradiology 20 years ago, prior to the development of CTA and MRA, and was functioning as a general radiologist in recent years. As the ordering physicians we have an obligation to provide the correct clinical history to the physician interpreting a test, i.e., “left third nerve palsy rule out posterior communicating artery aneurysm,” and to make sure that a qualified radiologist has reviewed the film. The technology exists for early diagnosis to dramatically reduce morbidity and mortality in aneurysmal third nerve palsy; we just have to implement it correctly.

Advances in technology have frequently affected clinical practice. An advance in the field of ophthalmology, optical coherence tomography (OCT), also has implications for neurology. With OCT very accurate measurements of either the macula or the retinal nerve fiber layer (RNFL) can be obtained and repeated over time. OCT in multiple sclerosis (MS) is used in 2 settings: patients with optic neuritis and patients without optic neuritis.⁸ When used in MS with optic neuritis the OCT shows thinning of the RNFL occurring in the involved eye about 3 months after the onset of an episode of optic neuritis. The amount of thinning correlates with visual function as measured by mean deviation on Humphrey automated perimetry. In patients with MS without optic neuritis there is also thinning, but to a lesser extent, of the RNFL over a 12-month or longer period. Thinning on OCT correlates with brain atrophy measures from MRI and with worsening of Expanded Disability Status Scale score. Loss of axons in the nerve fiber layer produces the thinning and this measurement seems to be a surrogate for disease activity. OCT is noninvasive, does not require dilation, and can be done in a few minutes for each eye. Unfortunately, there are no validated treatment strategies or paradigms (yet) to say when to change treatment based on change in OCT RNFL measurements. OCT might be useful as a measure of success in clinical trials, assuming the trials go for a long enough period of time to be able to see and affect RNFL change.

While the role of OCT is still under investigation in MS there are several conditions where OCT data can be very helpful. Vigabatrin is known to cause visual field loss in a significant

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- Values for normal intracranial pressure in children
- A possible infectious etiology for giant cell arteritis
- Radiologist accuracy in diagnosing aneurysmal third nerve palsy
- Role of OCT in MS, vigabatrin toxicity, and optic nerve glioma
- Genetic testing in congenital cranial dysinnervation syndromes

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number of patients, and visual acuity and visual field monitoring is recommended. In a study of 201 patients on vigabatrin changes in RNFL thickness were well correlated with visual field loss.⁹ Given that up to 20% of adult patients and children under 10 cannot accurately do visual field tests OCT can be used to follow changes in RNFL thickness as a surrogate for changes in visual field testing. Optic pathway glioma is another condition in which monitoring of visual function is critical to treatment decisions. In optic pathway glioma, with or without neurofibromatosis, RNFL thickness on OCT correlates with visual functioning. In this population of patients who lose vision at an average age of 4.9 visual function testing of even acuity, much less automated perimetry, can be very difficult. In a study of 89 patients with optic pathway glioma 41 had visual loss correlating with thinning of the RNFL.¹⁰ Patients with an optic pathway glioma are typically followed until there is documented visual loss or significant radiologic change and then chemotherapy is started. Visual loss can occur without radiologic change so both parameters need to be followed. Given the young ages of these patients the decision to start treatment is not an easy one. Having an objective test that can be used in a population that has difficulty with standard subjective testing can greatly facilitate care of these patients.

A number of cranial nerve syndromes have been known and described for many years including Duane retraction syndrome types I, II, and III and Mobius syndrome. Other ocular motility abnormalities thought to be from muscle abnormalities have also been known for many years including congenital fibrosis of extraocular muscles and double elevator palsy. Recent work with families with multiple affected members has led to the discovery of genetic mutations responsible for these syndromes, recognition that they are neural in origin, and development of a group of disorders called congenital cranial dysinnervation disorders (CCCD).¹¹ In CCCD, there are conditions in which ocular motility is primarily affected, including Duane type I and III, Mobius syndrome, congenital fibrosis of extraocular muscles types 1, 2, and 3, and horizontal gaze palsy with progressive scoliosis. Hereditary congenital ptosis and hereditary congenital facial palsy are CCCD syndromes with normal ocular motility. A variety of other symptoms, limb abnormalities, and cognitive disorders can be seen with some of these syndromes. When seeing patients with these findings there is now a framework to better classify and genetically diagnose these conditions. As genetic testing advances, our ability to accurately diagnose and provide prognostic information both for the patient and potential offspring will continue to improve.

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DISCLOSURES

Dr. Cornblath reports no disclosures relevant to the manuscript.

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