Neuromyelitis Optica: Mayo Clinic Blood Test Supports Clinical Diagnosis

One patient has uncontrolled vomiting. Another patient has eye pain and blurry vision that quickly progresses to blindness. Another has weakness and spasms of the legs. All three patients test positive for the neuromyelitis optica (NMO) antibody. NMO is a demyelinating disease that affects the optic nerves and the spinal cord. It can lead to blindness, paraplegia, bladder and bowel dysfunction, respiratory failure, and death. For nearly 100 years, NMO, also known as Devic’s disease, was considered a variant of multiple sclerosis (MS). There was no effective diagnostic test or treatment. The story of how NMO came to be differentiated from MS is a tale of turning accepted dogma on its head. It is a story in which the diagnostic criteria for NMO were redefined, the first biomarker for an inflammatory demyelinating central nervous system (CNS) disease identified, a blood test developed, and an intervention strategy established. It is a story that is still being written, with implications for treating autoimmune-mediated CNS conditions using targeted therapies. It is a story made possible only in the context of the free flow of information between clinical practice and basic science.

Identifying the Biomarker That Redefined NMO

From his extensive clinical experience, Brian G. Weinshenker, MD, a neurologist at Mayo Clinic in Rochester, Minnesota, had long suspected that Devic’s disease was a separate entity. In 1999, he and one of his neurology colleagues, Dean M. Wingerchuk, MD, presented retrospective data on 60 cases at Mayo Clinic whose profile appeared to distinguish NMO from MS. In the audience, Vanda A. Lennon, MD, PhD, a Mayo Clinic research immunologist, was struck by the fact that NMO patients often had accompanying autoimmune disorders that are not part of the MS profile. She asked Dr Weinshenker to send some serum samples from his patients to her laboratory. What Dr Lennon discovered was a previously undescribed antibody that attached to a component of the mouse blood-brain barrier in a similar pattern as samples that she had archived from patients who had been tested to rule out a paraneoplastic disease. Checking back with referring physicians, she and Dr Weinshenker discovered that all 12 of the cases whose histories they could acquire had optic neuritis and myelitis. What they realized is that they had found the antibody for Devic’s disease was first made by Sir Thomas Albutt in 1870. In 1894, Eugène Devic and Fernand Gault described 16 cases, from which the diagnostic criteria were taken. For the next 105 years, recognition of Devic’s disease was frozen by a rigid and arbitrary set of diagnostic criteria. Most cases that were relapsing with “lesions disseminated in time and space” also satisfied the criteria for MS and were accordingly labeled MS. This dogma persisted throughout the 20th century, despite debate over observations that acute episodes were more immediately devastating than in MS, the lesions were fewer and rarely found on MRI of the brain, and therapy for MS was unsuccessful in Devic’s disease.

Describing the Biomarker

Figure 1. The target molecule of the neuromyelitis optica (NMO) antibody, NMO–immunoglobulin G (NMO-IgG), is aquaporin-4. This molecule occurs in particles and clusters that reside on the end-feet of the astrocytes which surround the blood vessels, the tight junctions of which constitute the blood-brain barrier. The astrocyte end-feet also encircle axons at the nodes of Ranvier. Mayo Clinic scientists suspect that damage to astrocyte end-feet by the NMO-IgG autoantibody contributes to myelin damage and also compromises the blood-brain barrier.
Devic’s disease. They labeled it NMO-immunoglobulin G (NMO-IgG).

At the same time, Claudia F. Lucchinetti, MD, a Mayo Clinic neurologist and MS investigator specializing in mechanisms of tissue damage in demyelinating diseases of the CNS, recognized a unique pattern of demyelination in NMO and proposed that NMO was an autoimmune disease that targeted the perivascular space. She published her findings in 2002. In 2004, the combined Mayo Clinic team published results of a prospective study confirming that NMO-IgG was specific for NMO. By 2006, Dr Lennon had identified the antibody target, a water channel protein called aquaporin-4, which is abundant in astrocytes in the CNS (Figure 1, see page 1). It is most strongly expressed in the medulla, spinal cord, and optic nerves—the areas most affected by NMO. Dr Lennon’s laboratory then developed a blood test for NMO-IgG that is 99% specific and 70% sensitive for NMO. The antibody is absent in patients with MS, including those with optic neuritis and myelitis.

Aquaporin-4 is the main channel through which water enters and leaves the CNS. It is neither a component of myelin nor expressed by oligodendroglial cells that produce myelin. Its discovery has opened up new ways of thinking about immunopathophysiological mechanisms of other demyelinating diseases, including MS.

**Diagnosis**

Misdiagnosis is a common problem in NMO. The presenting symptom in 10% of cases is vomiting or prolonged hiccups (reflecting medullary involvement), for which neurologic disease is rarely suspected. The optic neuritis and myelitis of NMO are often confused with those of MS. The defining features of NMO are transverse myelitis and optic neuritis with at least two of the following characteristics:

- MRI results nondiagnostic for MS
- A spinal cord lesion extending over three or more vertebral segments (short segment lesions are typical of MS)
- A serologic test result positive for NMO-IgG

Early diagnosis of NMO is critical. In MS, individual inflammatory episodes are usually mild. Their cumulative effect over time causes progressive disability. In NMO, the opposite is true; acute episodes are usually severe and, if untreated, can have devastating, irreversible effects on function. Episodes may occur from days to years apart.

Seventy percent of NMO patients have relapses after their initial symptoms.

NMO can affect children as young as 3 years and adults as old as 90 years. MS predominates in whites, but NMO affects all ethnic groups and is as common among nonwhite persons as it is among whites. NMO is far more prevalent in women than men. Its onset is typically ten years later than MS (average age of onset, 39 years).

**Blood Test**

Because NMO-specific lesions may not be evident on MRI, a blood test result that is positive for NMO-IgG enhances diagnostic accuracy. Mayo Clinic in Minnesota, where the test was developed, is currently the only laboratory in the United States that offers it (Figure 2).

However, Mayo Clinic has licensed the technology to facilitate the development of test kits for use in laboratories worldwide. Of the 1,000 tests conducted per month at Mayo Clinic, approximately 70 results are positive. For the 30% of patients who have NMO symptoms but yield a negative test result, periodic retesting is recommended. Complementary second-generation tests are reducing the percentage of NMO patients with results negative for NMO-IgG.

**Treatment**

At Mayo Clinic, patients who test positive for NMO-IgG after an acute episode are treated immediately with drugs to prevent future relapses. To facilitate recovery from an acute attack, the first line of treatment is usually a short course of intravenous corticosteroids. Plasmapheresis can be used to remove the antibody from the blood when corticosteroid therapy is not successful. The effects can be dramatic. Immunosuppressants, which are not generally used as first-line drugs in MS, appear to reduce the frequency of future episodes of NMO.

**Future Directions**

Since Mayo Clinic’s pioneering work on NMO in 2004, researchers at other institutions have confirmed Mayo Clinic’s findings. In addition to Drs Lennon, Lucchinetti, Weinshenker, and Wingerchuk, the Mayo Clinic NMO team includes Charles Sean J. Pittock, MD.
L. Howe, PhD, a neurobiologist; Istvan Pirko, MD, a neurologist with expertise in inflammatory CNS demyelinating diseases and CNS imaging of animal models; and Sean J. Pittock, MD, and Andrew McKeon, MB, BCh, neurologists with expertise in translational research. Together, the Mayo investigators are conducting a multipronged NMO research program (Figure 3) that includes the following areas:

- Epidemiology
- Genetics
- Investigations of mechanisms of tissue injury
- Development of animal models to investigate the basis of NMO-IgG effects on myelin and gray matter injury and to explore new therapeutic approaches
- Development and validation of new diagnostic and prognostic tests
- Therapeutic trials in NMO

The synergy between Mayo Clinic’s clinical practice and its laboratory science has redefined NMO and its spectrum of disorders and continues to inform the development of targeted treatment options.

Treating Trigeminal Nerve Pain

The stabbing, lancinating, recurrent facial pain associated with trigeminal neuralgia (TN) is considered one of the most painful sensations in human experience. It occurs in the distribution of the trigeminal nerve, is of sudden onset, and is excruciating. It can impact mood, sleep, overall health, and employment and, in some cases, has led to suicide.

Management of TN and other types of neurologically based facial pain is best served by a team approach with close communication between neurologists and neurosurgeons, who together can provide various treatment options. Treatment ranges from drug therapy to surgery. Therapeutic success is particularly dependent on differential diagnosis to distinguish classic TN from other types of facial pain, some of which share clinical features with TN.

Differentiating TN From Other Types of Facial Pain

TN can occur at any age but is most common after age 50 years, with a higher incidence rate in women than men. Its most distinguishing clinical feature is the nature of the pain. In an effort to elucidate its etiologic features, experts recently subcategorized TN into TN1 and TN2.

TN1, or classic TN, generates repetitive volleys of piercing, paroxysmal pain that can last seconds or minutes and sometimes hours. It is almost always unilateral and typically occurs in the mandibular and maxillary divisions of the trigeminal nerve. TN1 can be triggered by everyday activities that stimulate the nerve, such as eating, speaking, or touching the face. Pain-free intervals range from several days to years, but typically the pain increases in frequency and severity over time. It is most often caused by vascular compression at the trigeminal nerve root. The redundant looping of an intracranial vessel (typically, an artery) that occurs with aging is thought to create pressure on the trigeminal nerve as it exits the brainstem. In rare cases, the nerve root may be compressed by a tumor, an
aneurysm, or an arteriovenous malformation. Over time, demyelination of the nerve due to compression may generate random, spontaneous afferent discharges.

The pain in TN2 is distinguished by a throbbing, burning sensation that is constant rather than episodic. TN2 can arise from various sources, including the following:

- Structural anomalies, such as tumors or arteriovenous malformations
- Inflammatory conditions, such as multiple sclerosis (MS) and herpes zoster
- Trigeminal nerve injury caused by stroke or dental procedures
- Deafferentation arising from intentional denervating procedures used to treat TN1 (eg, anesthesia dolorosa)

Often, TN2 is misdiagnosed as dental pain, for which patients undergo needless tooth extraction. Some patients with TN2 report the shooting pain of TN1 as occurring within a background of chronic dull pain that is more characteristic of TN2. In MS, the symptoms may be the same as in TN1, but the cause is entirely different.

Although demyelinating disease and structural anomalies may be evident on high-resolution MRI, neurovascular compression may not always be seen. For this reason, the clinical examination is critical in determining the best approach to treatment.

**Treatment Options**

Mayo Clinic takes a patient-centered approach in which the patient participates in the decision process leading to treatment. William P. Cheshire Jr, MD, a neurologist at Mayo Clinic in Florida, says, “We try to bring the pain under control with medication first, but treatment depends on a variety of factors, including age and health status. For example, if medication isn’t helping, a patient may be looking at years of intractable pain, so a surgical approach may offer the best long-term option.”

Richard S. Zimmerman, MD, a neurosurgeon at Mayo Clinic in Arizona, adds, “Medication is always the best way to start, but an older patient may be concerned about drug interactions or side effects. However, some patients are anxious to avoid invasive procedures.”

Fredric B. Meyer, MD, a neurosurgeon at Mayo Clinic in Rochester, Minnesota, notes that patients benefit from working with a neurologist who is willing to try a number of different medications and dosing. “At Mayo,” he says, “we are fortunate to have neurologists who specialize in face pain and to have all the medical and surgical options available under one roof.”

**Medical Management**

In TN, the goal of pharmacologic intervention is prevention. TN1 does not respond well to analgesics but does to antiepileptic drugs such as carbamazepine, sometimes at lower doses than those used to treat epilepsy. Usually, pain control can be determined within a few days, but over time the effect may wear off. As Dr Cheshire notes, dose titration is an art. Incremental dosing helps to prevent dose-dependent adverse effects that might discourage patients from continuing a pharmacologic approach when it could be of great benefit.

**Surgical Management**

Depending on the probable cause of TN, surgical options include microvascular decompression for classic TN1 (Figure 1, see page 3) and percutaneous denervating procedures or stereotactic radiosurgery to block the pain signal. For cases of microvascular compression, surgery directed at the site of compression (Figure 2) can stop the pain immediately and have excellent long-term durability.

Percutaneous ablation techniques, such as balloon compression or the injection of alcohol into the nerve (glycerol rhizotomy), are less invasive but also are less durable because the nerve may recover over time. Stereotactic radiosurgery, another ablative technique, is the least invasive surgical approach, with excellent outcomes. Motor cortex stimulation is not used for TN1, but it has been found effective for selected cases of intractable trigeminal neuropathic pain arising from deafferentation or previous nerve injury in TN2.

**Figure 2. Trigeminal nerve and arterial loop (left panel) and the same area after surgical decompression (right panel).**
Stereotactic Radiosurgery Is Safe and Effective for Selected Children With Arteriovenous Malformations

Mayo Clinic found that Gamma Knife stereotactic radiosurgery is a safe and effective option for selected children with arteriovenous malformations (AVMs). Researchers said that Mayo Clinic’s 20-year experience with AVM radiosurgery has shown that risks commonly associated with radiation exposure in children and adolescents are extremely low. The study was presented at the American Association of Neurological Surgeons Annual Meeting. Authors: B. Pollock, M. Link, and P. Schomberg.

Researchers Find IDE Gene Expression Levels Alter Risk of Alzheimer’s Disease


Stereotactic Radiosurgery Successful for Most Patients With Large Acoustic Neuromas

A Mayo Clinic study found that Gamma Knife stereotactic radiosurgery is a well-tolerated, successful treatment for the majority of patients who have large acoustic neuromas. However, in patients with large acoustic neuromas, the rates of cranial nerve disability and tumor progression are higher than in patients with smaller tumors. This study was presented at the American Association of Neurological Surgeons Annual Meeting. Authors: B. Milligan, R. Foote, B. Pollock, and M. Link.

American Academy of Neurology Meeting

Mayo Clinic neurologists were involved in nearly 100 platform and poster presentations at the 2010 American Academy of Neurology Meeting held in Toronto, Ontario. Three of those abstracts are noted below. In addition, three Mayo Clinic neurologists presented at full-meeting plenary sessions: Thomas G. Brott, MD, on the “CREST Trial”; Gregory A. Worrell, MD, PhD, on “Devices for Epilepsy”; and David W. Dodick, MD, on “Contemporary Clinical Issues and Case Studies.”

New Insight Into Tissue Damage in Multiple Sclerosis

A Mayo Clinic study found that the type of tissue damage changes throughout the course of multiple sclerosis. In early relapsing disease stages, the plaques are predominantly active with distinct heterogeneous patterns of myelin damage. In the chronic progressive phase of the disease, smoldering and inactive plaques predominate and are characterized by a uniform pattern of tissue damage. Authors: C. Lucchinetti, J. Frischer, J. Parisi, S. Weigand, K. Thomsen, W. Brueck, H. Lassmann, and J. Mandrekar.

News Coverage Biased Against Drivers With Epilepsy

A Mayo Clinic study found that newspaper coverage is biased against people with epilepsy in reporting of auto crashes. Researchers at Mayo Clinic in Arizona said that the public has misconceptions about people with epilepsy and their ability to drive. The study pointed out that drivers with epilepsy have only a 1/500 to 1/10,000 increased risk of crashes compared with the general public. However, newspaper coverage has created a “perceptual mismatch” between statistics and general awareness. Authors: S. Zarkou, J. Drazkowski, K. Noe, M. Hoerth, and J. Sirven.

Exercise and Computer Use May Reduce the Risk of Mild Cognitive Impairment

Mayo Clinic researchers found that physical exercise and computer use may help protect against mild cognitive impairment (MCI). In previous studies, both physical exercise and cognitive activities (including computer use) were separately found to help reduce the risk of MCI. In this new study, the combination of these two activities appears to be even more beneficial. Authors: Y. Geda, R. Roberts, D. Knopman, T. Christianson, V. Pankratz, B. Boeve, R. Ivnik, E. Tangalos, W. Rocca, and R. Petersen.

To read more about Mayo Clinic neurosciences research and patient care, visit www.mayoclinic.org.
Redefining Non-Alzheimer’s Dementias: New Protein-Based Diagnostic Categories

Among the general public, the deteriorating cognitive skills associated with the dementias are typically interpreted as memory loss and labeled Alzheimer’s disease. However, non-Alzheimer’s dementias (NADs) constitute a separate group of dementing illnesses that differ from Alzheimer’s disease in pathogenesis and behavioral consequences. Research over the past decade has shown that although some NADs may affect memory, memory loss is not a principle component of these diseases. Depending on the syndrome, the principle symptoms may be aphasia, apraxia, personality changes, impaired executive function (problem solving), loss of object knowledge (agnosia), psychosis, and movement disorders. NADs are thought to be as prevalent as Alzheimer’s disease in people less than 65 years of age.

Subsumed under the category called frontotemporal lobar degenerations, NADs share many histopathological characteristics and biochemical abnormalities. They also share certain clinico-pathological features with some extrapyramidal syndromes and motor neuron disease (Figure, see page 7). The result has been substantial category overlap and syndrome confusion.

Keith A. Josephs, MD, a Mayo Clinic neurologist, and his colleagues are dedicated to refining and redefining these subcategories. Their work, funded by the National Institutes of Health, is based not only on behavioral symptoms, but also on imaging and newly identified protein-based mechanisms. Already, it has led to more precise prognosis and improved genetic counseling and is helping patients and families plan for the immediate and long-term future. Equally important, it is preparing the way for targeted molecular treatments.

Unique Approach to Differential Diagnosis
At Mayo Clinic, diagnosis of NADs takes a unique approach. It is based on pattern recognition—a pattern that combines detailed behavioral, motor, and speech-language assessment with the results of MRI and PET imaging. From these results, Dr Josephs generates probabilities about underlying protein pathology on the basis of large clinicopathological studies.

Trained in movement disorders, pathology, and behavioral neurology, Dr Josephs is particularly well qualified to diagnose NADs. His team of collaborators includes Dennis W. Dickson, MD, a neuropathologist at Mayo Clinic in Florida, and, at Mayo Clinic in Rochester, Minnesota, Joseph R. Duffy, PhD, and Edyth Strand, PhD, in speech pathology; Jennifer Whitwell, PhD, and Clifford R. Jack Jr, MD, in neuroimaging; and Dr. Joseph’s behavioral neurology colleagues.

Teasing apart the clinical presentation of NADs is complex. Symptoms may overlap across syndromes, and apparently unrelated symptoms may emerge within a syndrome as disease progresses. The key is determining the prominence, as opposed to the presence, of a symptom at a given stage in the disease. For example, as Dr Josephs and his colleagues have reported, corticobasal syndrome (CBS) often begins with a prominent and isolated apraxia of speech (a nonaphasic speech-motor-programming deficit). Several years later, as speech continues to deteriorate, patients may have dystonia of the arm and alien limb syndrome. Although the symptoms appear to affect different parts of the nervous system, they are usually caused by a single protein aberration.

Major Syndromes

Frontotemporal Dementia
Frontotemporal dementia (FTD) is an umbrella term that encompasses three major syndromes: behavioral variant FTD (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). These syndromes are distinguished by their dominant presenting features:

• bvFTD: prominent changes in behavior or personality, accompanied by executive dysfunction; may include less dominant language impairments
• SD: loss of word knowledge and object knowledge (agnosia) and varying degrees of facial recognition impairment (prosopagnosia) predominate; additional behavioral changes may occur with prominent right temporal lobe involvement
• PNFA: aphasias with agrammatic or telegraphic speech output; rarely includes behavioral and personality changes; as disease progresses, extrapyramidal symptoms may appear

Extrapyramidal Syndromes
PNFA, bvFTD, and SD may all have extrapyramidal symptoms, and the syndromes may overlap with progressive supranuclear palsy syndrome (PSP-S) and CBS. The dominant symptoms of PSP-S and CBS are the following:

• PSP-S: akinesia, rigidity, vertical supranuclear gaze palsy, balance problems, apraxia of speech or dysarthria, and generalized apathy; behavioral and personality changes may occur but are mild
• CBS: asymmetrical akinesia and rigidity, apraxia of speech, aphasia, dysarthria, limb apraxia, myoclonus, and alien limb phenomenon; behavioral and personality changes also may be prominent

FTDs may also include features of motor neuron disease (MND) with the bulbar symptoms of speech and swallowing difficulty, weakness, spasticity, fasciculations, hyperactive reflexes, clonus, and a Babinski sign. Motor neuron signs are rarely associated with SD, PNFA, or PSP-S but may be found with a bvFTD-like syndrome. When motor neuron signs are involved, the syndrome is called FTD-MND.

**Imaging**

Patterns of atrophy that appear on MRI or hypometabolism on PET scans help to distinguish affected areas in FTD syndromes and related dementias. The patterns are the following:
• bvFTD: bilateral frontal and anterior temporal lobes and striatum
• SD: bilateral, middle, inferior, and medial anterior temporal lobes, typically asymmetrical
• PNFA: left posterior inferior frontal lobe (perisylvian region)
• PSP-S: midbrain tegmentum and superior cerebellar peduncle
• CBS: posterior superior frontal lobe; sometimes extends into the superior parietal lobe

**Molecular Mechanisms and Genetics**

As Dr Josephs points out, there appear to be associations between clinical syndromes and biochemistry, with some associations stronger than others. Several protein aberrations have been identified as the pathological mechanism for NADs. TDP-43, a protein important in DNA transcription and alternative splicing, is implicated in most FTD syndromes that previously lacked distinctive histologic features. It is associated with bvFTD, SD, PNFA, and FTD-MND, although accurate biomarkers are still being sought.

Abnormal accumulation of the microtubule-associated protein tau (MAPT) is linked with PSP-S and sometimes with CBS and bvFTD, which are called tauopathies. More than 90% of FTDs and related disorders can be classified as either a variant of TDP-43 proteinopathy or a tauopathy. Very recently, the protein FUS (fused in sarcoma) has been implicated in three additional types of NAD.

Patients with NADs may have a family history that suggests a genetic underpinning. Mutations have been identified in five genes, although most mutations that are identified have been in the progranulin (GRN) gene or the MAPT gene. These two genetic variants have been associated with specific clinical syndromes and imaging signatures. Mutations in MAPT are more commonly associated with bvFTD and temporal lobe atrophy; mutations in GRN are associated with PNFA and CBS, show more asymmetrical changes, and tend to affect the parietal lobe.

**Clinical Implications**

Dr Josephs notes a recently examined patient who had an isolated apraxic dysgraphia. She could print words but had difficulty writing in cursive. Speech pathology testing identified no speech or language impairments. Given the patient’s clinical presentation and PET scan findings, she was further tested and found to have a positive result for a specific gene mutation with high penetrance that predicts she has a TDP-43 proteinopathy, a finding with implications for her and her offspring.

NADs may generate symptoms that are not as easily understood as the memory loss in Alzheimer’s disease. For example, prosopagnosia may be the issue in failure to recognize family members. In some NAD syndromes, patients may believe that their spouse has been replaced by an identical-looking impostor (Capgras syndrome). Apraxia of speech, which affects speech output, can exist in the context of unimpaired language skills or can be the initial presentation of PSP-S and is highly predictive of a tauopathy.

In addition, NAD syndromes progress at different rates. Some cases, like those of SD, have a survival of approximately 10 years, compared with cases of FTD-MND, which have an average survival of 2 years—a difference with important implications for long-term care.

By drawing biochemical, imaging, and behavioral symptom associations, Dr Josephs and his colleagues are helping patients and families understand the implications of previously poorly understood dementing illnesses. As they continue to redefine syndrome criteria, they are also setting the stage for future targeted intervention.
Expedited Patient Referrals to Mayo Clinic Departments of Neurology and Neurologic Surgery

While Mayo Clinic welcomes appointment requests for all neurologic and neurosurgical conditions, patients with the following conditions are offered expedited appointments:

1. Cerebral aneurysms
2. Cerebral or spinal arteriovenous malformations
3. Brain, spinal cord, or peripheral nerve tumors
4. Epilepsy with indications for surgery
5. Carotid disease

Interested in receiving Mayo Clinic neurology and neurosurgery news in your inbox?
Go to www.mayoclinic.org/publications/medicalprofs-enews.html to sign up for Mayo Clinic’s Physician Update - Neurosciences e-mail newsletter.

Upcoming Conference

Mayo Clinic has a long history of commitment to managing facial pain. Several of its neurosurgeons are members of the Medical Advisory Board of the Facial Pain Association (formerly the Trigeminal Neuralgia Association). On August 28-29, 2010, in Rochester, Minnesota, Mayo Clinic will sponsor the association’s 20th Anniversary National Conference (visit www.tna-support.org for more information).