Neuromyelitis Optica

NMO

What You Need to Know

A guide for patients, their families and caregivers

THIRD EDITION

EDUCATION • RESOURCES • RESEARCH • AWARENESS

Providing information and support for those living with NMO

You may have NMO –
but NMO does not have you.

Welcome. You are not alone...

You have taken the first step with us by saying yes to a cure.

When Ali was diagnosed with NMO in 2008, there was next to no information available for anyone facing what at that time was a poorly understood autoimmune condition. When we learned how little was being done to advance basic and clinical science toward solving NMO, The Guthy-Jackson Charitable Foundation was formed. We said yes to funding the research needed to better understand, treat, and ultimately cure NMO. We gathered the best and brightest experts in many disciplines and they said yes—to leading us on a life-saving path of progress.

In preparing this 3rd Edition of our ***NMO Patient Guide***, we are more inspired than ever by all the members of our NMO community—especially the scores of patients who have said yes to sharing your stories and your clinical data. Together we have made great strides on our mission to solve NMO. From the new diagnostic criteria that improve the speed and accuracy of NMO and NMOSD diagnosis, to exciting clinical trials studying new drugs to prevent relapses, we are making a difference. When patients participate in formal clinical trials, they are helping to develop safe, effective and approved treatments. And when patients and families donate blood to the CIRCLES program, they are helping to unlock the mysteries to solving NMO.

To date, over 15,000 readers have eagerly reached for prior editions of our ***NMO Patient Guide***. We gratefully receive many thoughtful words of appreciation, along with reports that convey a global connection among those who live with NMO. Together we continue to raise awareness of this rare disease. Together we say yes to breakthroughs that will unlock solutions for NMO patients, and for patients suffering from autoimmune diseases, who number as many as 30 million in the U.S. alone, and hundreds of millions worldwide.

Our ***NMO Patient Guide*** is intended to inform and inspire all those who have been affected by NMO.

With love and hope,
Victoria Jackson and Ali Guthy, Founders

You Are the Cure

A decade ago, only a handful of specialists had even heard of NMO—this rare and orphan condition in which many patients are often first diagnosed as having multiple sclerosis or other diseases. That all changed with The Guthy-Jackson Charitable Foundation and its mission to cure NMO.

Together with countless patient heroes, their families and a laser-focused NMO research consortium, the Foundation united a global team of problem-solvers to decode the mystery of NMO. From state-of-the-art laboratories to leading drug companies, these efforts have forever changed the landscape of NMO science and medicine. These steps from molecules to miracles are told in ***The NMO Story*** and ***NMOtion*** features.

Many patient-inspired milestones have been achieved on this mission to cure NMO, including:

- NMO research publications have risen from less than 550 as of 2007 — to over 4,000 as of 2017
- Today, the GJCF international clinical consortium links 79 members from 24 countries worldwide
- We now know NMO is due to autoreactive T and B cells, autoantibody, complement and leukocytes

- In 2015, the International Panel for NMO Diagnosis (IPND) rewrote the book on NMO diagnosis
- Based on IPND criteria, NMO is now estimated to be 50 percent more common than previously known
- New diagnostic criteria have improved diagnostic speed & accuracy for NMO and related diseases
- NMO is now clearly differentiated from MS in terms of causes, effects, diagnosis and clinical care
- Two distinguishable forms of NMO have been characterized: AQP4-reactive and MOG-reactive
- Gender, race, geography and other factors are now known to contribute to NMO epidemiology
- CIRCLES, the largest multi-center NMO study, is on its way to its goal of 1,000 NMO patients enrolled
- Key genes that appear to influence NMO risk have been identified and are now being investigated
- Biomarkers are emerging as predictive signals of pathogenesis, relapse and treatment outcomes
- Today, multiple clinical trials are underway to find safe and effective new treatments for NMO
- Over 10 drug targets have been discovered in NMO, creating a pipeline for next-gen treatments
- The Foundation is now catalyzing a bold new science of tolerization to cure NMO permanently

There is more to do to solve NMO—and only patients can provide the X factors for cures. They hold the keys—their courage and optimism inspire us to find them. Like patients, we have made ending NMO personal.

Combining rare hearts with rare minds is how every patient, advocate, researcher and industry and regulatory partner has helped the Foundation revolutionize the field of NMO—it is a model that is redefining how information can be shared, answers can be found and lives can be saved.

Breakthroughs made to help solve NMO have also sparked a bold new movement to solve other diseases—rare and not so rare. From multiple sclerosis, diabetes, lupus and like autoimmune diseases—to cancer, heart disease, infection, wound healing, transplantation and aging—secrets of the immune system learned from NMO shine a bright new light to help meet the greatest challenges in human health.

Extraordinary people inspire extraordinary achievements. Whether through clinical trials, research, advocacy, sharing your story or raising funds, everyone can participate in the cure for NMO. ***You Are the Cure.***

With heartfelt thanks to every NMO patient, family, caregiver, researcher, clinician and stakeholder —

Dr. Michael Yeaman
Chair, GJCF Advisor Team

Using This Book

This guide may be a companion, a mentor, a compass, a friend – all meant to support you on your journey with neuromyelitis optica (NMO) and/or neuromyelitis optica spectrum disorder (NMOSD). Refer to section 1.7 for more information about the distinction between NMO and NMOSD. While certain sections address NMO and NMOSD specifically, for simplicity in this guide, the abbreviation NMO will be used to include both NMO and NMOSD. Whether you are a patient, a caregiver, a family member, a friend, or someone who just wants to learn more about NMO, we hope that you can find some answers to unanswered questions, a helping hand where there was no help. Perhaps its contents will encourage patients and all stakeholders to gain comfort and knowledge from the resources in this guide and in the foundation's online community. Because this book offers a great deal of information, we encourage you to pace yourself. In navigating the world of NMO, we hope this guide may serve as an interactive tool that will aid living with NMO until there is a cure. You may have NMO – but NMO does not have you.

To address primary concerns of NMO patients, their families and caregivers, information is presented in a format to best assist newly diagnosed as well as established patients. The content lists at the beginning of each section aim to assist in finding specific information.

This book provides information intended to help everyone best meet the unique challenges of living with an uncommon disease. Ask your doctor for advice regarding questions that arise as you read this book.

Valuable companions to this guide include:

- The Guthy-Jackson Charitable Foundation website: **guthyjacksonfoundation.org**
- **NMO Resources**, the free smartphone app for NMO and NMOSD **smarturl.it/nmoresources**

There you will find ways to help cure NMO by educating yourself about or participating in NMO clinical trials, joining the CIRCLES study and biorepository, learning of the latest scientific discoveries, and engaging to the NMO community through social media like Facebook and Twitter. Patients and caregivers may gain from these opportunities by connecting with others who are living with NMO. Other helpful resources include:

- **NMOTV** – a library of videos and multimedia tools to understand NMO in many different ways

- **Spectrum** – a library of published NMO studies that highlight the exciting new discoveries emerging from NMO research
- **Connect the Docs** and **Mapping NMO** – assist in locating NMO clinicians and our community of NMO Advocates
- **NMOtion** – (pronounced "in motion") tools and resources targeting NMO advocacy, education, and raising general awareness about NMO
- **LEAD** – an educational program empowering patients to educate themselves about NMO and opportunities to participate in the cure
- A link to our **donation page** for those who are able to contribute to NMO research. Any donation amount is welcome and appreciated on our mission to cure NMO. **The Guthy-Jackson Charitable Foundation allocates 100 percent of all donations directly to NMO research.**

The Guthy-Jackson Charitable Foundation is proud to facilitate awareness and education about NMO.
It is important to note that information provided in this resource guide should not be used or considered as clinical advice, therapeutic recommendations, or medical treatment. For specific information and medical advice, consult your physician. The Guthy-Jackson Charitable Foundation does not endorse or recommend specific products, services, manufacturers, or assume any liability whatsoever for the use or content of this or any product or service mentioned.

Contents

Preface

A diagnosis of neuromyelitis optica (NMO) and/or neuromyelitis optica spectrum disorder (NMOSD) can be confusing and frightening for patients and loved ones. Many newly diagnosed patients may feel overwhelmed, powerless, and afraid. The resources contained in this guide are intended to empower all those affected by NMO — and help NMO patients and their families understand that you are not alone – others travel this road with you. While certain sections address NMO or NMOSD specifically, for simplicity in this guide, the abbreviation NMO will be used to represent both NMO and NMOSD.

How many people have been diagnosed with NMO? This answer remains difficult to know precisely. However there is emerging evidence that the number of cases is considerably higher than known to date. This situation may be due to a previous lack of awareness of the disease, limited test methods that did not allow accurate diagnosis, and similarities that NMO shares with other autoimmune and neurologic conditions. Current studies indicate that the ***incidence*** (number of new cases) and ***prevalence*** (total number of known active cases) of **NMO are significantly greater than originally estimated.** Importantly, NMO is now becoming more effectively diagnosed thanks to new diagnostic methods, laboratory tests, and special imaging methods. Many of these tools have emerged in just the past several years, so the current estimates of NMO disease almost certainly do not reflect the actual incidence and prevalence of NMO worldwide.

Historically, the prevalence of NMO was estimated to be approximately 1-4 per 100,000. Today, due to improved awareness and advances in clinical diagnosis, research data estimate that NMO afflicts up to **10 in 100,000** persons. **This rate suggests nearly 15,000 NMO patients in the U.S. alone, and hundreds of thousands of patients worldwide.** Interestingly, the prevalence of NMO appears to vary in different regions and among distinct populations around the world. Because such population effects may result from heritable or environmental factors, this observation may provide new insights into the genetic contributions to NMO.

NMO is one of roughly **7,000 rare diseases** that affect about **30 million people in the U.S. alone**, and up to **700 million individuals worldwide**, according to the **National Institutes of Health (NIH)** and **World Health Organization (WHO)**. Each rare disease touches a relatively small population, making it difficult to recover research costs of developing treatments. Rare diseases are often called **orphan diseases** because they have not been adopted by the pharmaceutical industry as a focus for drug development. **However, NMO is special even among rare**

diseases, because there is a simple blood test that can enhance diagnosis and aid potential therapeutic development. This test is called the **NMO-IgG assay,** which determines whether an individual has detectable autoantibody in their blood or cerebospinal fluid that targets the **aquaporin-4 (AQP4)** protein. In this guide, details are provided about this test, and where it can be accessed.

While a diagnosis of NMO can be challenging, it can also reveal great strengths. When faced with their teenage daughter's diagnosis of NMO, the Guthy-Jackson family set out on a mission on behalf of all those affected by this uncommon disease: to catalyze groundbreaking research to accelerate treatments and cures. By forming The Guthy-Jackson Charitable Foundation, research was launched to facilitate prevention, diagnosis, treatment, and quality of life for NMO patients and caregivers. To do so, the Foundation brought together scientists and clinicians, pharmaceutical and biotech companies, governmental agencies, as well as patients and families to explore ways to cure this disease.

The Guthy-Jackson Charitable Foundation (GJCF) is a non-profit 501(c)(3) organization dedicated to funding breakthrough research, increasing public health education, and bringing physicians and researchers together to develop safe and effective treatments and ultimately find a cure for NMO.

To facilitate these goals, the GJCF has assembled leading scientific and medical teams that have published the latest scientific and clinical guidelines. The Foundation

has also established expert clinical centers for NMO research (called CIRCLES sites; refer to Chapter 5). The GJCF has also directly funded innovative basic and clinical science to better understand causes and effects of NMO, and in turn, improve NMO diagnosis and treatment. The GJCF promotes collaboration among scientific, clinical, industry, and regulatory partners to accelerate new medical solutions and end NMO once and for all.

NMO patients and their blood relatives are invited to talk to their clinicians and caregivers about the possibility of volunteering to participate in clinical research. **Everyone can play a role in curing NMO.**

NMO Explained

1

NMO Explained

1.1 What is NMO?

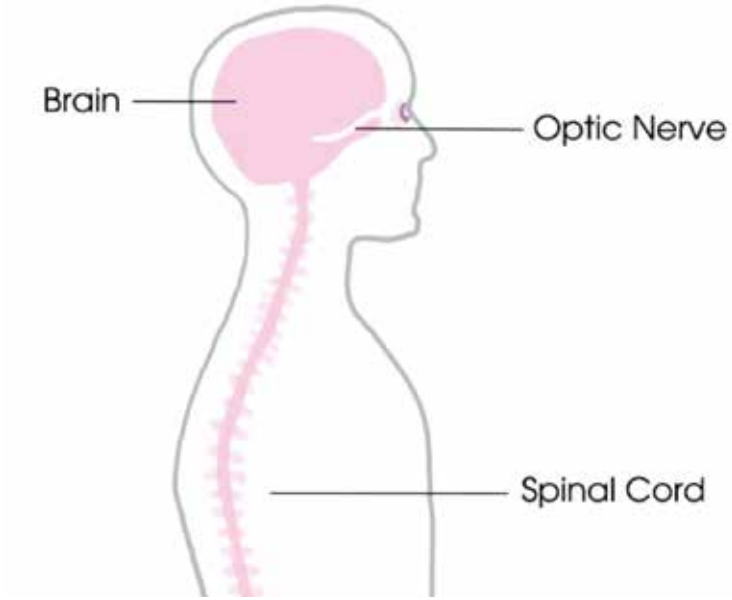
Once thought to be a type of **multiple sclerosis** (MS), **neuromyelitis optica** (NMO) and **neuromyelitis optica spectrum disorder** (NMOSD) are variants of a distinctive but rare autoimmune disease. Today, NMO and NMOSD occur when the immune system mistakes normal tissues of the **central nervous system** (CNS) as being foreign. As a result, the immune system attacks these tissues, making proteins (called **antibodies**) and recruiting immune system cells that can harm otherwise

healthy parts of the CNS. Often, because CNS tissues are rich in a protein called aquaporin-4 (AQP4), **the initial attack targets the nerves of the eyes and other parts of the CNS, which include the brain and spinal cord.**

QUICK READ

Neuromyelitis optica (NMO) and **NMO spectrum disorder (NMOSD)** are diseases that damage tissues of the **central nervous system (CNS)**. These conditions likely result from dysfunction in the immune system such that it reacts to otherwise healthy, "self" tissues. This mistaken identity causes injury and swelling (**inflammation**) of the optic nerves (**optic neuritis or ON**) and/or spinal cord (**transverse myelitis or TM**). The first symptoms of NMO are often changes in vision (light perception or acuity), eye pain, loss of balance, and/or numbness or weakness of the feet, legs, arms, or hands. These symptoms may improve, but can reappear (**relapse**) and may worsen over time.

NMO is an inflammatory disease of the CNS characterized mainly by attacks (**relapses**) of swelling and damage in the optic nerves (optic neuritis or ON) and spinal cord (transverse myelitis or TM). Normally, nerve cells (neurons) depend on special cells called **astrocytes** for survival and function.



When astrocytes are injured by autoantibody directed against the AQP4 protein, as occurs in NMO, the nearby neurons can also be damaged directly or due to inflammation. In turn, injured and inflamed neurons can lose function, causing vision impairment or loss (ON), as well as imbalance, incontinence, weakness, numbness or paralysis of limbs or other body parts.

Astrocyte and neuron damage can also cause **demyelination**. This process erodes the protective **myelin sheath** covering that insulates nerve cells. Damage to myelin slows or stops nerve impulses traveling to or from the brain which may affect many physical systems. Some patients diagnosed with NMO may have attacks that affect certain parts of the brain, especially at the connection point of the spinal cord to the brain itself, a location called the **brainstem**.

1.2 What is the NMO-IgG biomarker?

A **biomarker** is a type of cell or molecule that is used to diagnose or predict a disease, or monitor how well a drug may be working to prevent a relapse or treat the disease. **In NMO, the immune system creates an autoantibody that targets the astrocyte water channel protein called aquaporin-4 (AQP4), a unique biomarker.** This special biomarker is called anti-AQP4 immunoglobulin G, or more simply **NMO-IgG**.

The GJCF is funding research to seek other important biomarkers to help prevent, treat or even cure NMO. Biomarkers may be found in some places in the body but not others. For example, certain types of cells and molecules pass through the **blood brain barrier** (BBB) and into the **cerebrospinal fluid** (CSF), while

others do not. So, particular biomarkers may be present in the CSF, while others are found only in the **peripheral bloodstream** (e.g. circulating blood as may be drawn from a vein in the arm). Some biomarkers change in concentration or location in the body over time. This fact may afford the opportunity to discover biomarker(s) to help guide safe and effective therapy, or perhaps even **predict when a relapse is going to occur**. If proven to reliably indicate or predict the diagnosis, disease status or severity, or a response to therapy, **NMO biomarkers can be important tools in preventing, treating or curing NMO**. Proving that a biomarker is specific to NMO or a key signal of the disease is a process called **validation**. This process must be carefully performed, and eventually approved by regulatory agencies for a biomarker test to be certified for use in the clinic.

To date, **the NMO-IgG test result is positive in ~75% of patients diagnosed with NMO.** Because **serum** is most often used to test for the presence of NMO-IgG antibody, a positive result is termed **seropositive**, while a negative result is termed **seronegative**. Among the ~25% of patients who are

To date, the NMO-IgG test result is positive in ~75% of patients diagnosed with NMO.

seronegative, there may be several reasons for such a result, including:

- the type of test (called an **assay**) used to detect the antibody was not effective (did not detect the antibody even though it may be present)
- the type of biospecimen tested (e.g. blood vs. CSF) did not contain any detectable NMO-IgG
- no NMO-IgG exists, suggesting an autoimmune process and/or auto-antigen different from NMO-IgG. For example, in some cases autoantibodies other than anti-AQP4 may be present (see below).

Although uncommon, **the assay results for NMO-IgG may change over time in some individuals**. For example, certain types of therapies may affect the ability of laboratory tests to detect NMO-IgG. Likewise, as assays improve, **NMO-IgG may be detected in some patients who have tested negative in the past**. This area of research is rapidly advancing, and may help uncover the causes and cures of NMO.

Anti-MOG antibody may be a new biomarker candidate in some NMOSD patients.

Do You Know...

The NMO-IgG test can be ordered by any qualified clinician. Today, there are many reference laboratories that can perform the test and report results within days.

Learn more about the NMO-IgG test and access the updated NMO diagnostic criteria on the GJCF website at:

guthyjacksonfoundation.org/diagnosis

One area of recent focus in NMO research is that of seronegative patients. New evidence suggests that antibodies to antigens other than AQP4 may exist in this group of patients. For example, antibody targeting **myelin oligodendrocyte glycoprotein (MOG)** appears to be present in some patients in whom NMO-IgG cannot be detected. This pattern suggests that **anti-MOG** antibody may be **a new biomarker candidate in some NMO patients**.

The GJCF supports breakthrough research to improve assay accuracy and reliability, understand where biomarkers are best found in the body, and explore **immune pathways** that may drive NMO disease regardless of whether it involves AQP4, MOG or other autoantibodies or targets of autoimmunity.

The NMO-IgG antibody test can be requested by any qualified clinician in the United States and many countries around the world. **The availability of the test is increasing globally due to collaborations in clinical research, and the launch of clinical trials evaluating drug candidates intended to achieve safe and effective treatment for NMO.** Individuals are encouraged to ask their doctor about the NMO-IgG test, as well as NMO clinical trials. For more information, please refer to section 1.7.

Learn More On
NMO Resources.

Download the app for free on your Android or iOS device today!

Available on the App Store

ANDROID APP ON Google play

Historically, NMO was most commonly diagnosed when both the spinal cord and optic nerves were affected, leading to vision problems along with limb weakness or paralysis. Yet, NMO may include more limited presentations that involve attacks of just one area (e.g. either ON or TM) with or without the AQP4 antibody. Research is quickly advancing, making it likely that diagnostic and therapeutic approaches to NMO will be further refined. Other conditions might also be considered as being within the definition of NMO. For example, inflammation of the brainstem that leads to **uncontrollable hiccups and nausea or vomiting**

that last for extended periods of time may be caused by NMO. The classification and diagnostic criteria regarding NMO are anticipated to evolve as new insights are gained and applied to improve patient care.

For simplicity throughout this guide, the abbreviation NMO is used to mean both NMO and NMOSD.

1.3 Are there different types of NMO?

QUICK READ

There are two forms of NMO based on recurrence:

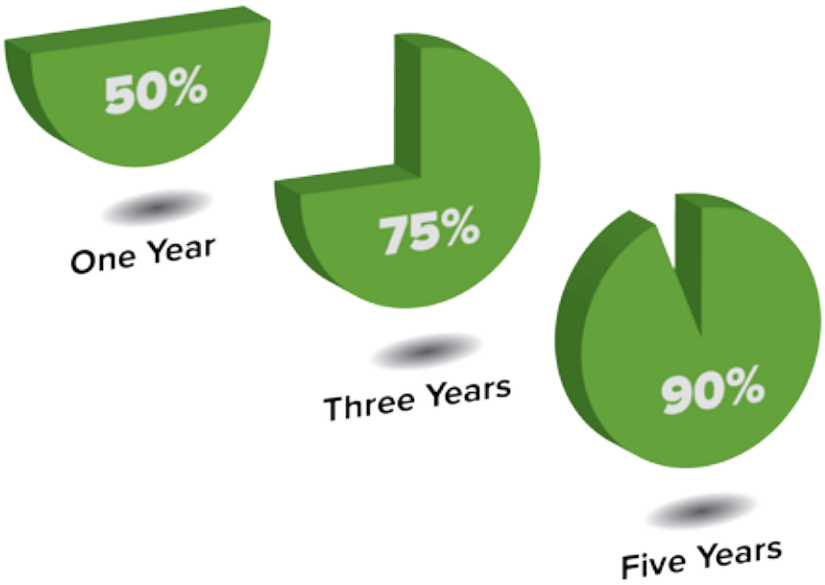
1. Relapsing NMO
2. Monophasic NMO

- **Relapsing NMO** is most common and identified by recurrent attacks separated by months or years. Attacks are usually followed by partial or complete recovery during periods of remission. **This relapsing form of NMO appears to affect women 4 times more commonly than men.** Unfortunately, in some severe cases of relapsing NMO, recovery may not occur following a relapse, causing permanent disability.

- **Monophasic NMO** is less common and is usually characterized by a single, severe attack over a short period of time (days or weeks). As a rule, relapses do not occur in monophasic NMO. This form of NMO typically affects optic nerve(s) and the spinal cord. Interestingly, women and men tend to be equally affected by this form of NMO.

When a patient is first diagnosed with NMO, it is unclear whether they will experience a monophasic or relapsing course. In either scenario, accurate and rapid diagnosis of relapses is a key to minimizing severity and promoting recovery.

Probability of recurrance among patients with relapsing NMO:



1.4 What causes NMO?

QUICK READ

The exact cause of NMO is unknown. As with many autoimmune conditions, NMO is likely caused by a combination of factors, and may be caused by different factors in different patients. Some of the factors being studied for potential contributions to NMO include:

- Genetics
- Co-existing Autoimmunity
- Infection or Vaccination
- Metabolic Disorders
- Endocrine Disorders
- Allergies
- Other Environmental Factors
- Combinations of the above

It should be emphasized that none of the above factors are known to cause NMO. Experts also do not know the causes of NMO relapses. The factors listed here, and detailed in the following pages, are among those on which research is being focused for their potential roles in this disease.

Genetics: Changes in structure or function of one or more genes may contribute to NMO disease. Such genetic changes may be present at birth, or

acquired over the course of one's life. Recent studies suggest that compared to Caucasian populations, people of Asian or African ancestry have a higher tendency to develop NMO. However, current research does not suggest heritability as a primary cause of NMO, nor is NMO significantly more common among relatives of NMO patients. It is estimated that 3 percent of patients have one or more family members affected by NMO, usually just a single individual. Although rare, NMO is more common than might be predicted by chance occurrence. This observation may suggest some genetic influences in the development of NMO. Careful research is being conducted to uncover new insights into possible genetic causes of NMO.

Co-Existing Autoimmunity: NMO is an autoimmune disorder. This means that the body's own defense system (**immune system**) attacks its own tissues and organs. In other words, the immune system turns on the body itself and causes disease. In NMO, the immune system is believed to target the **aquaporin-4**

Sometimes patients with one kind of autoimmune disease also develop other autoimmune diseases. This situation is termed co-existing autoimmunity, and may occur in NMO.

protein (AQP4) that is enriched on cells called **astrocytes** in the **central nervous system** (CNS). Currently, researchers believe that astrocyte injury and inflammation leads to loss of the myelin sheath that protects nerves (a process called **demyelination**), and results in CNS symptoms commonly present in NMO. Sometimes patients with one kind of autoimmune disease also develop additional autoimmune diseases, and this may be true for NMO. Approximately one-quarter of patients with NMO, especially those with a positive blood test for AQP4 autoantibodies (see section 1.7), also have one or more other autoimmune diseases, such as systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroid disease or myasthenia gravis.

Infection or Vaccination: The causes of NMO are currently unknown, and at present no infection or vaccine is known to cause NMO or relapses.

Hypothetically, there are many possible **triggers** of NMO, but **there is no clear evidence to prove any specific causes**. NMO researchers are open-minded to all possibilities for understanding how NMO begins and relapses occur in patients. Interestingly, it is possible that the initial causes of NMO and the triggers of NMO relapse may not be identical, and may be different from patient to patient. Some patients report having what they believe to be a respiratory, urinary tract, or flu-like infection prior to a relapse. While it is possible that

infection or vaccination may influence relapse, there is no proof of any cause-and-effect relationship in this regard to date. The causes of NMO and relapses are likely complex, and could involve many factors, including patient genetics, diet, hormone status, microbial flora (the **microbiome**), emotional stresses and many other factors. Furthermore, different factors may contribute to NMO onset or relapse in different patients. Studying the potential causes of NMO in a careful and evidence-based manner is the most responsible way to find meaningful answers and is a key mission of the GJCF.

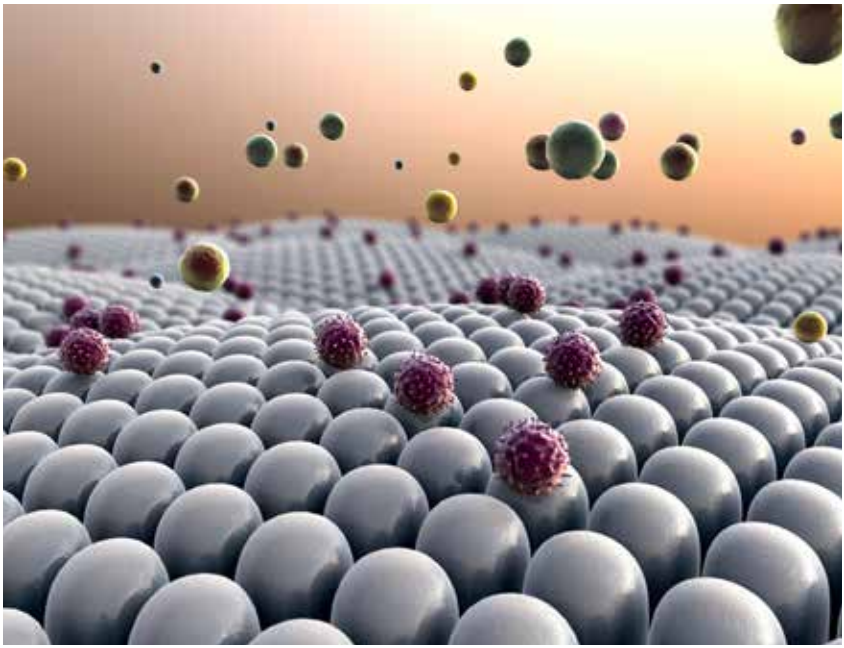
It is important to note that vaccination remains among the most effective ways to prevent many serious medical conditions, and to date the benefits of immunization programs far outweigh any known risks. Even so, it is best to consider vaccines carefully with respect to the specific needs, medical history and potential risk factors in each individual. **As with all information in this guide or elsewhere, NMO patients or anyone considering vaccination should consult with their physician or NMO specialist to assess the potential benefits or risks of vaccines that may be recommended.**

Metabolic Disorders: In recent years, certain autoimmune conditions have been suggested to be associated with metabolic disorders. For example, type-1 diabetes (T1D) is due to an autoimmune process in which the immune system attacks cells in the pancreas that make insulin. As a result, T1D can affect the

metabolic status of the patient. While unknown, it is possible that NMO may arise from a process that involves **metabolic dysfunction**, and NMO may contribute to such dysfunction. Some researchers believe that certain foods, including high-salt or sugar-rich diets can contribute to a general increase in **inflammation in the body**, or perhaps autoimmune diseases. One interesting area of current research focuses on food components as they may affect the microbiome of a person as potentially contributing to NMO or other autoimmune diseases.

Endocrine Disorders: NMO and most autoimmune diseases occur at a **much higher frequency in women than men**. This fact suggests there are unique aspects of gender that may contribute to autoimmune diseases, including NMO. For example, **hormones that differ in females and males** can influence the immune system, particularly during child-bearing years in women. Likewise, pregnancy can alter immune system function, and influence NMO onset or relapse frequency or severity. Research is in progress to better understand potential relationships among gender, hormones, pregnancy (refer to section 3.4), and NMO causes or relapses as compared to other related autoimmune conditions.

Allergies: Excessive or misdirected immune system responses are involved in allergies, as they are in autoimmune diseases. It is possible that there may be a common factor connecting these two conditions, which may contribute to NMO onset or relapse. This area of



research is a focus of studies that are currently ongoing. One exciting area of research involves treatments to reset the immune system in NMO and other autoimmune diseases, similar to methods used to solve allergies. For NMO, this strategy is called **tolerization therapy**. If successful, restoring immune tolerance in NMO has the **potential to solve the disease**, without the need for long-term immunosuppressive therapy. Minimizing or eliminating the need for long-term immunosuppression is important to reduce risks of infection, cancer or other conditions associated with such treatments.

Other Environmental Factors: Environmental factors may also contribute to the risk of NMO onset, relapse or severity. For example, the potential roles

of smoking, stress (physical and emotional), fatigue, temperature, geography, environmental pollutants or toxins, and other factors are being explored for potential impact on NMO through clinical science called epidemiology. In such studies, many different variables may be examined for potential correlations to NMO risk or relapse.

1.5 What are the symptoms of NMO?

QUICK READ

Common symptoms of NMO may include:

- Eye pain or an "eye headache"
- Changes in vision (light, color, or clarity) due to optic neuritis (ON)
- Numbness or weakness in limbs due to transverse myelitis (TM)
- Imbalance, dizziness, or pins-and-needles sensations
- Loss of bowel or bladder control

The symptoms of NMO can vary from person to person in disability, duration and severity. However, NMO is most commonly characterized by **optic neuritis (ON)** that affects eye function, and/or **transverse myelitis (TM)** that affects limb function.

Generally, NMO symptoms begin rapidly. After the initial attack, **NMO follows an unpredictable course**, and **time to remission can vary**. Recurring episodes of optic neuritis and/or transverse myelitis can be weeks to months in duration, and in some very unusual cases can last years. However, much more often these symptoms are temporary and resolve fully or partially, usually after a course of treatment.

Symptoms and signs of optic neuritis (ON) may include:

- Rapid onset of eye pain or "eye headache" that is worsened by eye movement
- Impaired or complete loss of vision usually in one eye, but in some cases in both eyes
- Reduced light perception, color vision, visual clarity, and/or depth perception

Symptoms of transverse myelitis (TM) include:

- Pain in the neck or back
- Tightness or corset-like sensations in the abdomen, as well as arms or legs
- Sensitivity to touch, cold and heat
- Feeling of numbness, tingling, coldness, itching or burning, often spreading to large parts of the body over a period of minutes, hours or occasionally days

- Weakness in arms or legs ranging from mild to complete paralysis in one or multiple limbs
- Urgent need to urinate or difficulty urinating; urinary incontinence (unintentional passing of urine)

- Constipation leading to vomiting, abdominal bloating, pain and inability to pass stool or gas; or bowel incontinence (unintentional passing of stools)
- Muscle spasms that may last for several minutes accompanied by arm or leg pain
- Fever in some cases

In cases of brainstem or brain involvement symptoms may include:

- Prolonged hiccups, nausea, vomiting or dizziness
- Mental confusion

1.6 What can I expect in the course of disease?

QUICK READ

NMO patients may experience any of the following:

- Acute attacks of ON or TM
- Rapid development of symptoms
- Potential plateau of symptoms
- Symptoms may improve over weeks and/or months with treatment

NMO is considered an acute disease because it **comes on suddenly**, **lasts a short time** and **may enter a remission**. Progressive disability developing over months and years is unusual. However, individual attacks may not be recoverable leaving severe neurological disabilities that are permanent.

NMO symptoms may develop quickly — **even within a few hours** — increase over the course of a few days and then plateau. Symptoms may improve over weeks and months with treatment. Lasting signs and symptoms of NMO may differ in each patient, and vary according to many factors, including:

- The severity and degree of recovery from the first attack
- The number and frequency of subsequent relapses
- The effectiveness of therapies

- Other co-existing conditions or autoimmune disorders, if they are present or develop
- Gender
- Age
- Pregnancy
- Other factors

Depending on the response to maintenance therapy, some patients will experience multiple attacks of ON and/or TM throughout their lives. **Some measure of improvement may occur, but patients may experience residual symptoms or disabilities that persist.** Based on current data, among patients with relapsing NMO, roughly **50 percent** will have one relapse in the first year after the initial episode, **75 percent** by the third year and **90 percent** by the fifth year. **The intervals between relapses are highly variable and unpredictable, but might**

The intervals between relapses are highly variable and unpredictable, but may be managed by adjusting medications that may help to prevent or delay relapses.

be managed by adjusting medications that may help to prevent or delay relapses. Relapses can be spaced months or years apart. Although the majority of patients facing NMO have a relapsing form of the disease, early diagnosis and treatment may reduce the relapse rate and/or lessen the severity of relapses should they occur.

While uncommon, patients with monophasic NMO tend to have a more severe initial attack than those with relapsing NMO. Approximately **20 percent** of patients with monophasic NMO have permanent vision loss, and **30 percent** have permanent paralysis in one or both legs. **In order to be classified as monophasic, no relapse may occur after the initial episode of optic neuritis and/or myelitis.**

New diagnostic criteria have provided specific definitions for NMO and NMOSD that facilitate consistency in defining disease and clinical care of patients. In this new diagnostic process, potentially confusing terminologies have been clarified so that a more accurate diagnosis can be made and appropriate treatment begun more quickly for most patients.

The fact that **monophasic NMO patients** have only one attack suggests that their immune systems may find a way to correct the dysfunction that caused disease. If so, **these patients may hold discoveries that could be key to understanding NMO and finding ways to stop it.** All NMO patients are encouraged to consider participating in research,

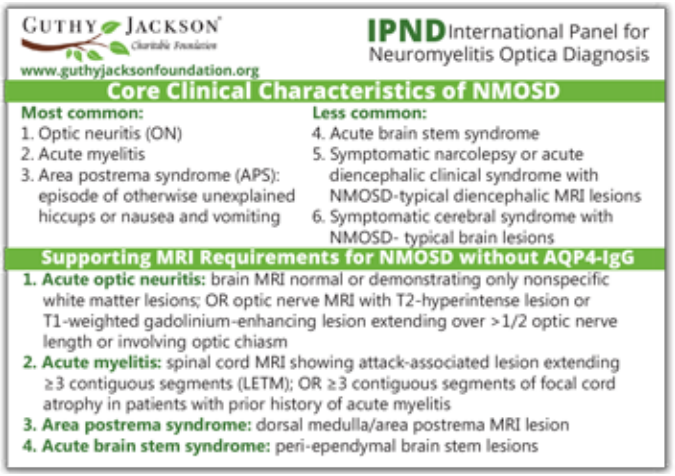
learning more about clinical trials to help find cures, and donating blood and clinical information to research programs like the **CIRCLES NMO Biorepository** (refer to Chapter 5 for more information).

1.7 How is NMO diagnosed?

QUICK READ

NMO can be diagnosed by a combination of methods, including:

- Blood test: NMO-IgG
- Magnetic Resonance Imaging (MRI)
- Neurological examination
- Lumbar puncture (spinal tap)
- Eye tests
- Optical Coherence Tomography (OCT)



2015 IPND Neuromyelitis Spectrum Disorder (NMOSD) Diagnostic Criteria

In 2015, a global team of experts working with The Guthy-Jackson Charitable Foundation published new guidelines for improved diagnosis of NMO. This team, known as the **International Panel for NMO Diagnosis** (IPND), created what is now known as the 2015 IPND diagnostic criteria for NMO and NMO spectrum disorder (NMOSD). Clinical research using these new criteria is already showing significant improvements in speed and accuracy of NMO and NMOSD diagnosis. These advances help patients receive the most appropriate care more quickly, and also help patients who do not have NMO in the same way.

The IPND was comprised of 18 expert members from around the world.

Core Clinical Characteristics

Most common:

- Optic neuritis (ON)
- Acute myelitis
- Area postrema syndrome (APS): episode of otherwise unexplained hiccups or nausea and vomiting

Less common:

- Acute brainstem syndrome (e.g. intractable hiccups, nausea, vomiting, dizziness or confusion)
- Symptomatic narcolepsy or acute diencephalic* syndrome with typical diencephalic MRI lesions
- Symptomatic cerebral syndrome with typical brain lesions

** The diencephalon is an associated group of structures in the brain, including the hypothalamus, thalamus, epithalamus (including the pineal gland) and the subthalamus. Collectively, these structures comprise the diencephalon, which serves key functions, including controlling many roles of the autonomic nervous system. The autonomic nervous system works automatically (known as unconscious function) to regulate critical body functions, such as heart rate, breathing, pupil response in the eyes, urination and bowel activity, and many other functions. The autonomic nervous system is often considered to have two components: the sympathetic nervous system (e.g. "fight or flight" response) and the parasympathetic nervous system (e.g. "digest and rest" effects). In these ways, the autonomic nervous system controls many unconscious functions and instinctive behaviors that can be affected by NMO.*

NMO when NMO-IgG Test Positive (Seropositive for Anti-AQP4 Antibody)

- At least 1 core clinical characteristic (see above), ***and***
- Positive test for NMO-IgG*, ***and***
- Exclusion of alternative diagnoses**

NMOSD when NMO-IgG Test Negative or Unknown (Seronegative for NMO-IgG Antibody)

- At least 2 core clinical characteristics (see above) resulting from 1 or more clinical attacks, ***and***
- At least one of the following: optic neuritis (ON), acute myelitis with LETM, or area postrema syndrome PS, ***and***
- Dissemination in space (≥2 different core characteristics), ***and***
- MRI requirements, if applicable (see below)
- Exclusion of alternative diagnoses**

In addition to the above clinical signs and symptoms, **magnetic resonance imaging (MRI)** may also be used to establish or rule out other features that may be associated with NMO, such as inflammation of the optic nerve(s) (e.g. in optic neuritis [ON]), longitudinally extensive transverse myelitis (LTEM; meaning a lesion on the spinal cord spanning more than 3 continuous vertebral segments), area postrema syndrome (lesions in the medulla and adjacent areas of the brain that may cause intractable hiccups, prolonged nausea / vomiting or like conditions), and other features consistent with NMOSD.

** Using best available detection method (cell-based assay strongly recommended)*

*** Evaluation for alternative diagnoses guided by "red flags"*

Wingerchuk DM, et al. International consensus criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-189.

Why were the new diagnostic criteria necessary?

In just the last few years, quantum leaps have been made in understanding what NMO is, and what it is not. For example, it is now clear that NMO and multiple sclerosis are very different diseases in terms of immune system causes and effects. In addition, previous diagnositic criteria were not as good at recognizing NMOSD or varying forms of NMO. For these reasons, new criteria were needed to recognize these advances so that diagnosis of NMO could be made more quickly and more accurately, enabling the most appropriate medical care as soon as possible.

How were the new criteria developed?

The GJCF catalyzed much of the research that led to better understanding of NMO basic science and evidence-based clinical diagnosis. It did so by bringing

scientists and clinicians together to think in new ways to recognize NMOSD. One of the special groups organized by the GJCF was the International Panel for NMO Diagnosis (IPND). In collaboration with GJCF and its advisors, the IPND worked for nearly two years to carefully review all the available scientific and clinical data to develop the new diagnostic criteria. Data reviewed included cases, experiences, MRI and other imaging results, and laboratory testing such as serology. **In 2015, the IPND Diagnostic Criteria were officially published, and have greatly increased the speed and accuracy of NMO and NMOSD diagnosis.** It is also important to note that the 2015 IPND criteria have also benefitted patients with diseases that might otherwise be misdiagnosed as NMO, and vice versa. In this way, GJCF efforts have helped patients with NMO as well as patients who have other related autoimmune diseases.

What are the key improvements in the new criteria?

The 2015 IPDN Diagnostic Criteria for NMO offer many advances to improve the accuracy of NMO diagnosis, including:

- The new criteria address NMO Spectrum Disorder (NMOSD), an umbrella term for NMO and variants encompassed under the expanded spectrum of NMO signs and symptoms
- NMOSD patients can be further specified based on NMO-IgG status, or the presence of other autoantibodies (e.g. anti-MOG-IgG)

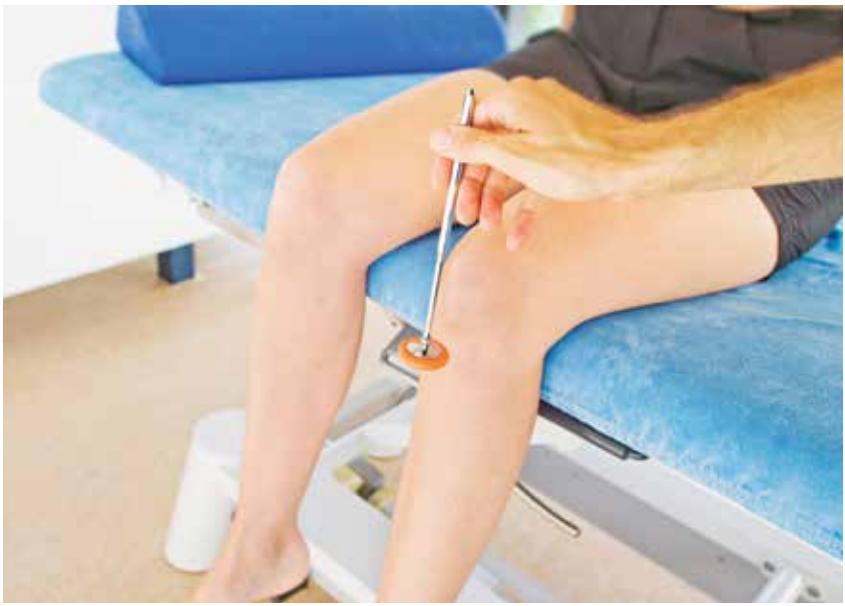
- Diagnosis can only be made in symptomatic individuals with compatible clinical presentations
- Clinical presentation is defined based on 6 core clinical characteristics that focus on neurologic features and their locations in the central nervous system (CNS)
- Only one core clinical characteristic is required in patients seropositive for NMO-IgG
- Criteria for NMO-IgG seronegative NMOSD are similar to those for seropositive patients, but include additional requirements for greater accuracy
- "Red flags" are also included in the 2015 IPND criteria, which indicated signs or symptoms that may suggest a diagnosis other than NMOSD. For example, clinical findings, imaging results and/or laboratory tests may raise concerns about NMOSD diagnostic accuracy and identify conditions that could be mistaken for NMO
- The new criteria also offer greater clarity in interpretation of NMO-IgG test results
- The criteria are more applicable to children, although there are special considerations for all pediatric cases. For example, caution is required regarding longitudinally extensive transverse myelitis lesions, which may also occur in children who have MS

Access the complete, open-source publication on the GJCF website at: guthyjacksonfoundation.org/diagnosis

What steps are involved in using the new diagnostic criteria?

A diagnosis of NMO begins with medical history, questions about signs and symptoms and a neurological examination. Key elements of diagnostic testing include:

- **Neurological Examination:** A key step in the process of diagnosing NMO is a thorough examination by a qualified neurologist or specialist in neurological diseases. The neurologist examines a patient for two types of signs and symptoms: 1) cognitive functions such as thinking, logic, memory and speech; and 2) sensory functions such as vision (acuity, depth perception, light perception, color, etc.), sensations such as touch, taste or smell, muscle strength, balance, reflexes, and coordination. An eye specialist (called a **neuro-ophthalmologist**)

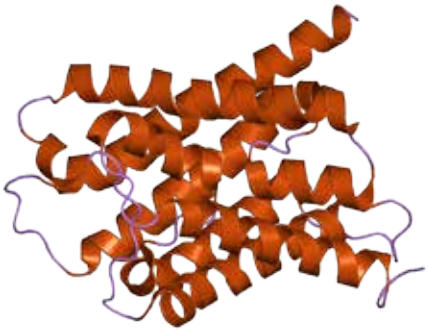


may also be involved in the examination to look for swelling or inflammation in the optic nerves or damage to the retinas.

- **NMO-IgG Blood Test (Anti-AQP4 Antibody Assay):** In approximately 75 percent of NMO patients, a specific **autoantibody** (a type of protein produced by **B cells** of the immune system) is present in the blood. This antibody can attack the **aquaporin-4** water channel protein normally present on healthy astrocyte cells of the central nervous system (brain, spinal cord, optic nerves). The blood test detects this **anti-AQP4 antibody,** which is known as **NMO-IgG** (NMO immunoglobin G). **The detection of NMO-IgG strongly supports a diagnosis of NMO.**

  However, not all patients with NMO have a positive NMO-IgG test. Someone may test

negative for NMO-IgG, but still have NMO or NMOSD. For example, it is possible that NMO-IgG may not be detectable with the test used, or the test may not be available in some places in the world.



Aquaporin-4 (AQP4)

Photo Source: By Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute - Public Domain, https://commons.wikimedia.org/w/index.php?curid=7137858

Also, some patients may have undetectable antibody levels due to treatment they are receiving. Recently, tests have been developed that have higher rates of detecting the NMO-IgG antibody (**sensitivity**) and accuracy to reduce the chance of false positive or negative results (**specificity**). It is possible that some NMOSD patients may be **seronegative** for NMO-IgG, but have a different autoantibody that may produce similar effects as NMO-IgG. For example, **anti-MOG antibody** may be present in certain NMOSD patients.

The **NMO-IgG test can be requested by any qualified physician** and is generally ordered by a neurologist or other specialist evaluating a potential case of NMO, NMOSD, or other related neurological condition.

- **Magnetic Resonance Imaging (MRI):** MRI is an important tool in diagnosing NMO. This **generally safe and painless test** uses strong magnetic fields and radio waves to produce a detailed **image of the brain and spinal cord**.

  In a typical MRI scan, patients are placed on a table that slides into a tube which houses strong magnets. Some centers have open MRI scanners (no tube) that are helpful for patients with claustrophobia. An MRI scan lasts approximately 30 to 60 minutes and requires the patient to be still the entire time. Often

a water-based dye (called contrast) is injected into an arm vein (through an IV or intravenous catheter) just prior to the scan. This dye allows for more specific pictures of the **lesions** or sites of inflammation in the brain, optic nerves and spinal cord and lasts in the body for only a few hours. In NMO patients, MRI test results often show lesions indicative of inflammation in the spinal cord, optic nerve(s) and occasionally in the brain. **However, brain lesions observed in NMO follow a different pattern and are not as common as in other diseases, including MS.**

- **Lumbar Puncture (Spinal Tap):** In some cases, a neurologist may request a lumbar puncture to sample **cerebrospinal fluid (CSF)** that bathes the spinal cord and brain. For example, if a patient has signs and symptoms of NMOSD, but has a negative blood test for NMO-IgG, diagnosis can be more accurate if CSF is tested for this or other autoantibodies.

In NMO, the cerebrospinal fluid (CSF) may show elevated white blood cell counts during first episodes or relapse attacks.

The lumbar puncture allows the neurological team to test the CSF for levels of immune cells, proteins and antibodies. In NMO, the spinal fluid may show elevated white blood cell numbers during attacks, which are greater than typically seen in other autoimmune diseases. In special tests to distinguish NMO from similar diseases, CSF is tested for **oligoclonal bands** (certain types of antibody groups), which are commonly detected in MS patients, and usually but not always absent in NMO patients.

- **Ophthalmological Tests:** To help obtain a correct diagnosis, patients may be referred to an ophthalmologist or neurological eye specialist known as a neuro-ophthalmologist. These experts may perform the following eye tests:

  A routine eye exam will check visual clarity (acuity), the ability to perceive different colors, and depth perception.

  Ophthalmoscopy examines the structures at the back of the eye such as the retina by shining a bright light into the area and using special lenses to view the structures. This eye test evaluates the optic disk

and fovea, which is the area where the optic nerve enters the retina in the back of the eye. The optic disk becomes temporarily swollen in about one-third of people with optic neuritis (ON). Patients who have had previous ON due to NMO may have a permanently pale optic disk, but the same signs may be present in patients with MS and other conditions that target the optic nerve. For these reasons, this finding is not specific for NMO.

Pupillary light reaction (PLR) tests the eyes to see how the pupils respond when exposed to bright light. After shining a bright light in a healthy eye, the pupil of the eye affected by ON often incorrectly dilates, likely due to inflammation or damage of the autonomic nervous system.

Optical coherence tomography (OCT) is a non-invasive image technique to study the retina.

OCT is a simple high-resolution scan used to measure the thickness of the retinal nerve fiber layer (RNFL). The RNFL may be decreased in NMO patients with optic neuritis.

1.8 Diagnoses Other Than NMO

QUICK READ

NMO can have signs and symptoms similar to:

- Multiple sclerosis (MS)
- Acute disseminated encephalomyelitis (ADEM)
- Sjögren's syndrome
- Systemic lupus erythematosus (SLE)
- Mixed connective tissue disease (MCTD)
- Infective inflammation
- Sarcoidosis
- Other neurological illnesses

With many signs and symptoms that are similar to those of multiple sclerosis (MS) or other neuroinflammatory conditions, misdiagnosis of NMO can be a missed opportunity to treat the disease in its earliest form and with the most appropriate medications. Conditions commonly confused with NMO that can produce optic neuritis and myelitis include:

- **Multiple sclerosis (MS):** an inflammatory condition of the central nervous system (CNS) affecting movement and balance. Like NMO, **optic neuritis and myelitis are common in MS, although generally less severe than in NMO**. In addition, MS usually has a slower, longer course of disability than NMO. **Unlike NMO, to date there is no blood test to diagnose MS.**
- **Acute disseminated encephalomyelitis (ADEM):** a short-term condition affecting the brain and spinal cord, which can also cause optic neuritis and myelitis.
- **Sjögren's syndrome:** an autoimmune condition typically affecting the salivary and tear glands.
- **Systemic lupus erythematosus (SLE):** an autoimmune condition causing joint pain, fatigue, rashes, kidney disease and sometimes inflammation in the CNS.
- **Mixed connective tissue disease (MCTD):** inflammation of the connective tissue associated with joint pain, muscle weakness, and in some cases damage to internal organs.

- **Infective Inflammation:** inflammation caused by an infection of the central nervous system (CNS).
- **Sarcoidosis:** a type of inflammation that may target multiple organs including the optic nerves, brain and spinal cord. Sarcoidosis that affects the CNS is called neurosarcoidosis.

FACTS ABOUT NMO AND MS

Until recently, NMO was thought to be a type of MS. However, recent discoveries have provided evidence indicating that NMO and MS are distinct diseases with distinct diagnostic criteria and treatment plans.

With so many symptoms in common, NMO can sometimes be confused with MS or other diseases. However, these diseases are treated in different ways and early detection and treatment help ensure best outcomes.

NMO symptoms may include:

- Severe, rapid onset attacks causing significant disability
- Episodes of prolonged nausea, vomiting or hiccups
- Usually normal MRI brain scan early in disease
- Distinctive lengthy spinal cord lesions
- NMO-IgG presence in blood and/or CSF

It is important

to emphasize that some MS medications do not help NMO patients, and may actually cause more severe attacks and complications in NMO.

Likewise, off-label treatments used for NMO may not benefit patients with diseases other than NMO.

These facts underscore the need for rapid and accurate diagnosis of NMO, as well as other similar diseases.

For more information, visit:
guthyjacksonfoundation.org/ms-nmo

MS symptoms may include:

- Initial attacks that are usually slower to emerge and relatively milder than NMO
- MRI which usually shows brain abnormalities in a recognized pattern
- Presence of oligoclonal bands in CSF of most MS cases but relatively few NMO cases; no NMO-IgG

1.9 Recognizing an NMO Relapse (Attack)

Mimicking the initial or onset episode, NMO patients can experience a recurrence of similar symptoms due to inflammation of the optic nerves and spinal cord as outlined in section 1.5. Such symptoms may also be after-effects of a prior episode, referred to as "ghost" or residual pain following an attack. It is important to determine whether such symptoms represent a new relapse, or the lingering effects of a previous attack. **Maintaining regular communication with your healthcare team, and seeing your physician or neurologist immediately if there are unresolved symptoms is best in this regard.**

1.10 Areas of the Body Commonly Affected by NMO

QUICK READ

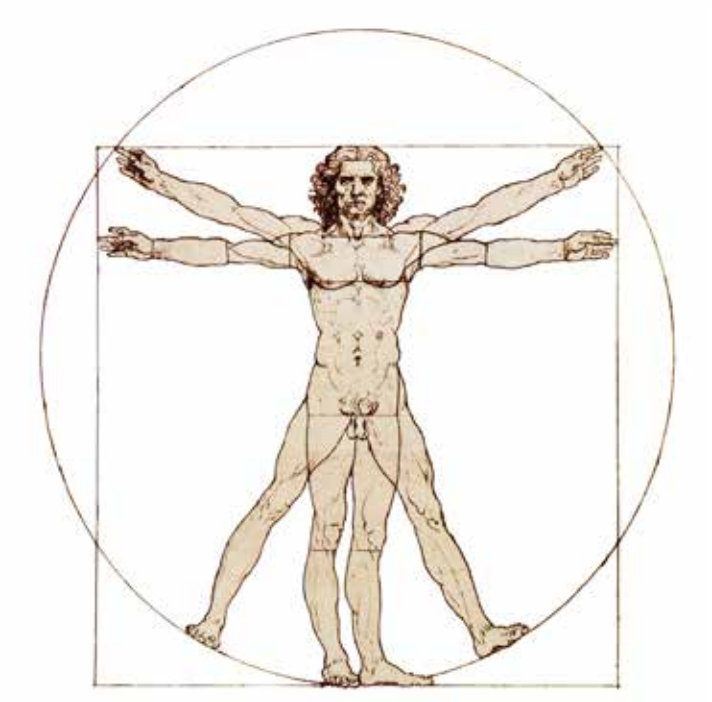
NMO occurs when the immune system (which normally protects against infection, cancer, and other disease) malfunctions. As a result, the immune system attacks healthy tissues, making antibody proteins and activating white blood cells that cause inflammation. In turn, these immune system factors damage the central nervous system (CNS) which leads to neurological problems.

Areas and systems of the body affected by NMO:

- Central nervous system (CNS)
- Peripheral nervous system (PNS)
- Blood brain barrier (BBB)
- Neurons
- Astrocytes
- Immune system

Nervous System

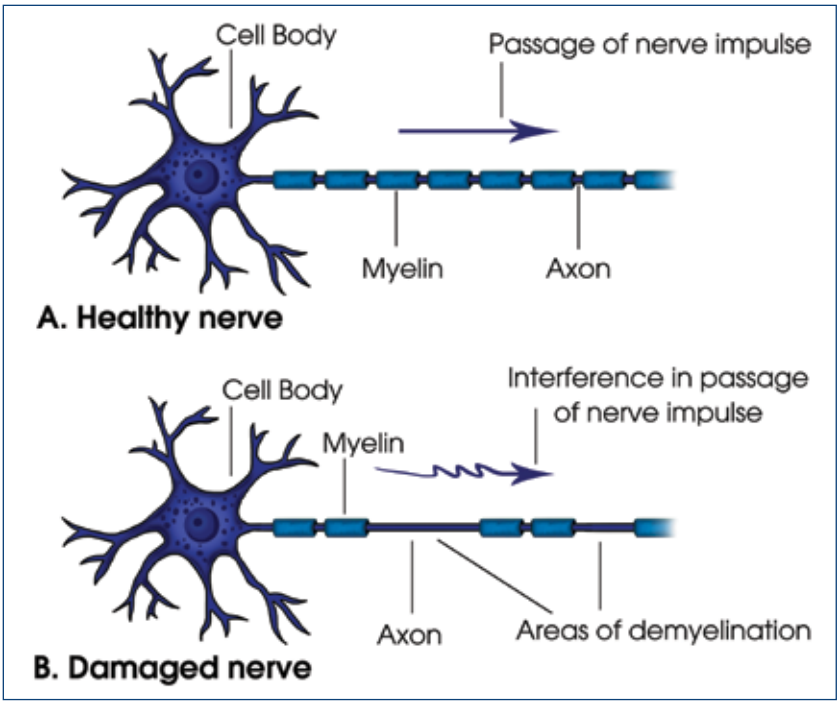
The nervous system regulates all body activity including memory, language, vision, mobility, and sensation. It includes the brain, spinal cord, optic nerves, and a circuitry of nerve cells (called **neurons**) responsible for transmitting information to and from all parts of the body. Other specialized cells known as **astrocytes** and **glial cells** structurally and nutritionally support the neurons.



The nervous system is comprised of the **central nervous system (CNS)** and the **peripheral nervous system (PNS)**. The spinal cord, optic nerves and the brain make up the CNS. They coordinate the activities between the various parts of the body. The PNS is the portion of the nervous system outside the brain and spinal cord. The PNS carries incoming messages to the CNS from sensory organs (such as the eyes, skin, and ears), and carries messages from the CNS to muscles, sweat glands, blood vessels and many other tissues.

The spinal cord and optic nerves are the main sites of the nervous system affected by NMO. The spinal cord controls movement, receives neuronal

signals and regulates bodily functions including excretions and secretions. The optic nerves carry visual information from the eyes to the brain. The CNS and PNS coordinate thought, logic, memory, balance, speech, bowel and bladder function, and many other essential bodily activities which can be affected by NMO.



Nerve Conduction

Neurons are the basic information processing units in the CNS. They receive, process and send information to other neurons through cable-like fibers called **axons** using special molecules called neurotransmitters.

Axons help process signals in the nervous system. For example, in the case of light stimulation, the eye collects the signal via the retina, which contains special sensors that convert light energy to neurotransmitter molecules. Next, these molecules activate neurons in the optic nerve, which in turn transmit the information to the brain. Similarly, in the case of pain stimulation, sensory information is carried from neurons in affected tissues to to the spinal cord and brain.

Axons are coated by a fatty substance called the **myelin sheath**, which plays an important role in speeding and securing electrical transmission along axons. This sheath allows impulses to transmit efficiently along the nerve cells (like insulation in an electrical system), ensuring messages sent by axons are not lost en route to the spinal cord, muscles or internal organs. **If myelin is damaged or removed due to inflammation, a process called demyelination, the ability of neurons to transmit signals slows down or stops altogether.** This effect can result in vision loss, limb weakness due to limited transmission of nerve impulses to and from the brain, or other loss in neurological functions.

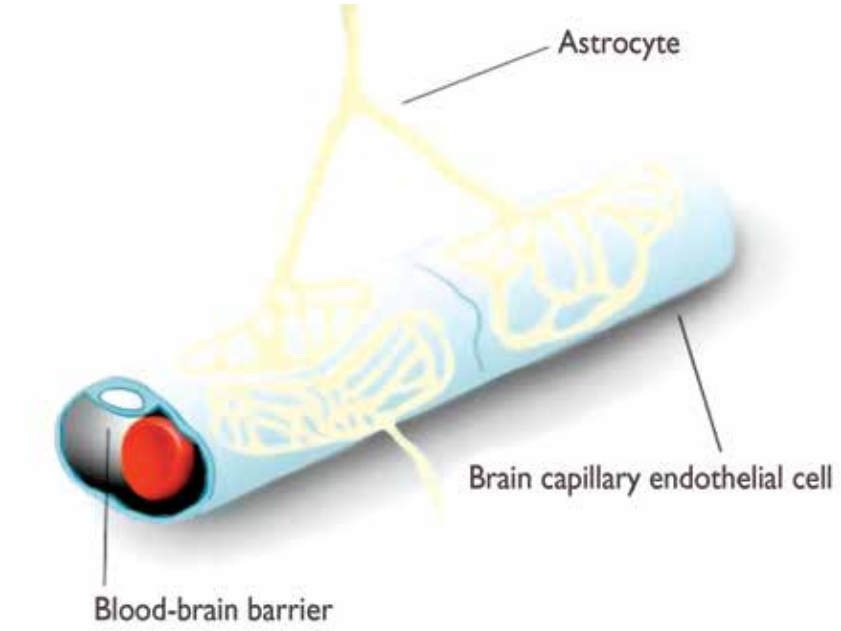
Blood-Brain Barrier (BBB)

The Blood-Brain Barrier (BBB) is a complex of cells and specialized proteins that interact where the central nervous system (CNS) tissues meet the blood vessels (capillaries). The BBB creates a filter to the CNS, separating the circulating blood and its chemical and

cellular components from the CNS. The barrier prevents some drugs, chemical compounds, radioactive ions, and disease-causing microbes that may be present in the blood from passing into the CNS. **The BBB helps protect the CNS from potentially harmful factors, including autoantibodies, circulating in the blood.** Only special cells and substances that provide food and function to the brain are allowed through the barrier. Some parts of the BBB are naturally more permeable (or easy to pass through), and **the NMO-IgG antibody appears to have a particular tendency to attack the brain at these more vulnerable sites of the BBB**.

Certain conditions may lead to breakdown of the BBB. When this happens, substances normally kept out of the brain are able to pass into the brain, spinal cord, or other components of the CNS.

Astrocytes



Astrocytes are the most abundant cells in the CNS and play key roles in the function of the BBB as well as neuron health. Astrocytes have several functions, including to serve as a framework guiding neurons to their proper locations during development, protecting and nourishing neuronal cells, and supporting the BBB to maintain a "privileged" environment unique to the CNS.

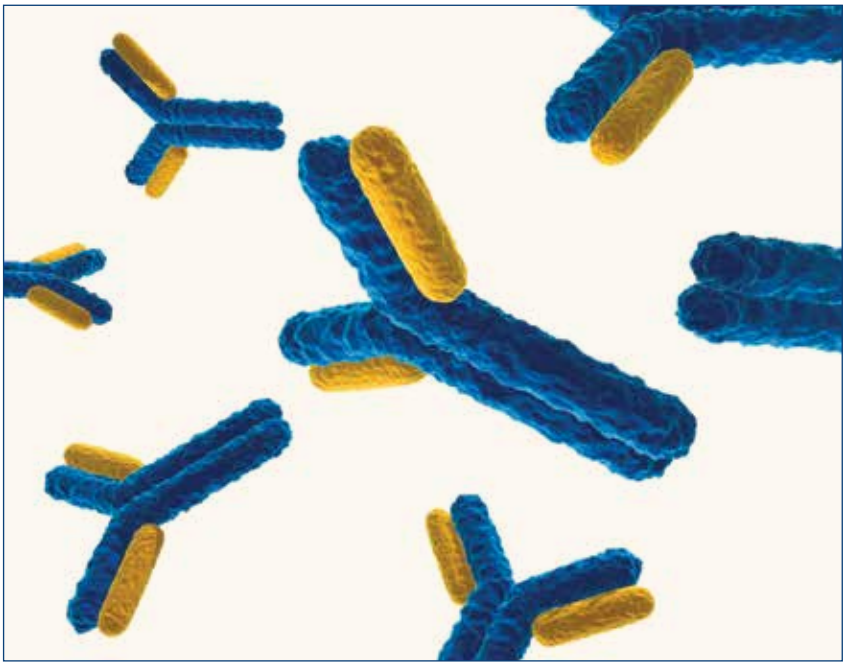
Astrocytes make other significant contributions to neuron activity including facilitating neurotransmission and signals for proper brain function and interaction with other CNS cells such as microglia.

Astrocytes also support water transport in the CNS through a special protein that spans from the surface of the cell, through their cell membrane, into the cell interior. This protein, termed **aquaporin-4 (AQP4)**, is a water channel that creates arrays of pores through which water flows in the cell. **In NMO, AQP4 is the target of NMO-IgG antibodies.** By attaching to the water channel AQP4 protein on the astrocyte, the antibody activates immune reactions, such as complement activation, and attracts inflammatory cells. In turn, such inflammation can lead to many adverse consequences by injuring, disabling, or destroying some astrocytes and disrupting the normal functions of others. Water flow through tissues is impaired when AQP4 protein is attacked, demyelination can occur, and the accumulation of immune cells and other factors at sites of astrocyte injury cause swelling due to inflammation. **Together, these processes may produce the symptoms of an NMO attack.**

You can learn more about clinical trials on our website at:

guthyjacksonfoundation.org/clinical-trials

The Immune System



Antibodies

One of the most important functions of the immune system is to defend the body from external threats such as microbes, or internal threats such as cancer. The ability to tell the difference between healthy cells and tissues, and those representing infective or cancer threats is key. The ways in which the immune system achieves this goal are complex. Simply put, the immune system **T and B cells** (also called **lymphocytes**) are responsible for detecting "self" (normal) and "non-self" (abnormal or foreign) molecules or cells. **B cells** are named for their maturation in the **Bone marrow,** while **T cells** mature in the **Thymus**. When a foreign (e.g. infecting microbe) or abnormal (e.g. cancer) cell is detected by

T and B cells, immune reactions are triggered. This step leads to activation and reproduction of the specific type of T and B cells that first recognized the threat. **Over time, these T and B cell lineages lead a coordinated immune response to specifically remove the foreign or abnormal target, such as the invading microbe or cancer cell.**

Most of the time the immune system is amazingly accurate in detecting foreign or abnormal cell threats and signals. However, in autoimmune diseases, this process goes wrong: T and/or B cells or other immune system cells mistake normal "self" tissues as foreign or abnormal.

NMO is believed to occur when the immune system attacks AQP4 and perhaps other "self" proteins, one's own tissues, as if they were foreign. Components of the immune system include the thymus and spleen, in which T cells and antibody-producing B cells mature in structure and function before graduating to protect the body from infection, cancer, and other diseases. Normally in this process, immune cells with abnormal function that mistakenly react to normal cells or tissues are deleted to prevent autoimmune diseases. However, this is not a fool-proof editing system, and certain **autoreactive (or autoimmune)** immune cells may survive and contribute to autoimmune disease.

NMO is believed to occur when the immune system attacks AQP4 and perhaps other "self" proteins as if they were foreign.

The ability of the immune system to recognize and ignore "self" tissues as being normal is called **immune tolerance**. When this normal process to protect against autoimmunity breaks down, the immune system reacts to otherwise healthy cells or tissues, and mistakenly attacks the body. The result is known as an autoimmune disease, or a disease where the immune system mistakes tissues of the body itself for a foreign or abnormal threat.

Such misdirected immune responses and resulting autoimmune diseases can cause a broad range of illnesses. In addition to NMO, hundreds of other autoimmune diseases are known, and **at the core of each of these illnesses is a loss in immune tolerance**. For this reason, GJCF is focusing special efforts in the exciting science of **restoring immune tolerance, or tolerization therapy, to treat or perhaps even cure NMO**. Most NMO patients have antibodies in their blood that target an ordinary protein on astrocytes of the CNS, AQP4. In NMO, tolerization therapy has initially been targeted to inhibit immune

cells that mistake AQP4 as foreign. **Catalyzed by GJCF, clinical trials are already beginning** and others are planned to apply the power of the immune system to solve NMO in a new era of restoring immune tolerance. **And if tolerization therapy succeeds in NMO, the same methods might be adapted to help treat or even cure many autoimmune diseases such as multiple sclerosis, type-1 diabetes, lupus, and beyond.**

1.11 How does NMO affect the body?

QUICK READ

In NMO, damage can affect the body if:

- The immune system mistakenly produces harmful AQP4 antibodies and inflammatory cells
- The Blood Brain Barrier becomes disrupted, allowing these factors to enter the CNS
- Complement proteins contribute to intense tissue destruction and attract other inflammatory components, such as white blood cells
- Inflammation leads to demyelination, which impairs functions of optic nerves, spinal cord and brain
- Further complications arise in the body, such as limb weakness or paralysis, bowel & bladder dysfunction, and other symptoms that are characteristic of NMO

In NMO, auto-antibodies targeting AQP4 and other self-proteins are mistakenly produced by the immune system.

Mechanisms of Damage

Inflammation

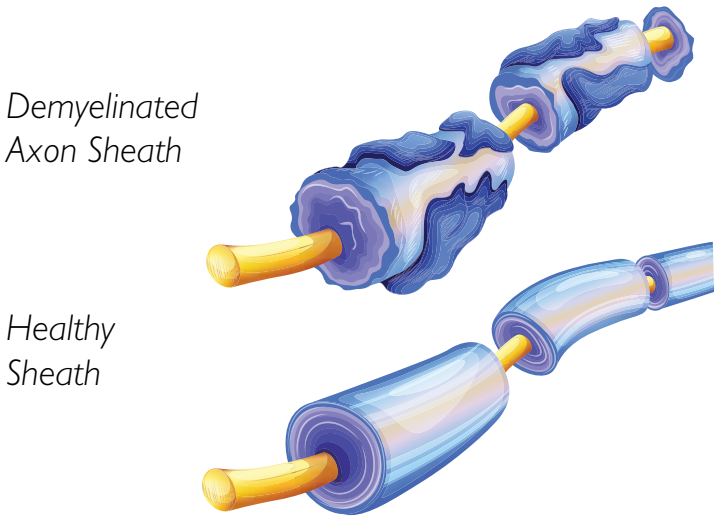
Inflammation is the first response of the immune system to tissue injury, infection, or other threat. For example, a cut to the skin will almost always result in inflammation, with its characteristic four signs: redness, swelling, pain, and heat. Inflammation is a vital defense mechanism essential for survival. Without inflammation, the body would not prevent blood loss at sites of injury, clear infection, remove harmful substances or allow normal tissue to rebuild. **In NMO, autoantibodies targeting AQP4 and other self-proteins are mistakenly produced by the immune system. These autoantibodies contribute to inflammation of the CNS that is a hallmark of NMO.**

Normally the blood-brain barrier (BBB) protects the CNS. However, if the BBB is disrupted or "opened" (see section 1.10), and AQP4 antibodies enter the CNS, they can attach to the AQP4 protein on the astrocytes. In

turn, this can send molecular messages to other white blood cells to attack the astrocytes. At the same time, another family of inflammatory proteins (called the **complement system**) is activated. Complement is a collection of over 20 proteins that work together and normally help immune system cells to clear infection, kill cancer cells, or promote wound healing. In the case of NMO, **complement proteins** can contribute to intense tissue destruction and attract other inflammatory cells, including special types of white blood cells called **granulocytes** (such as **neutrophils** and **eosinophils**) and **macrophages**.

Demyelination

When the AQP4 antibody interferes with the transfer of water in the brain, and activates immune system inflammation, water and immune cells and molecules accumulate near the astrocytes attacked in the CNS. In turn, the **myelin sheath** (protective insulation of neurons) can degrade, leading to **demyelination**.

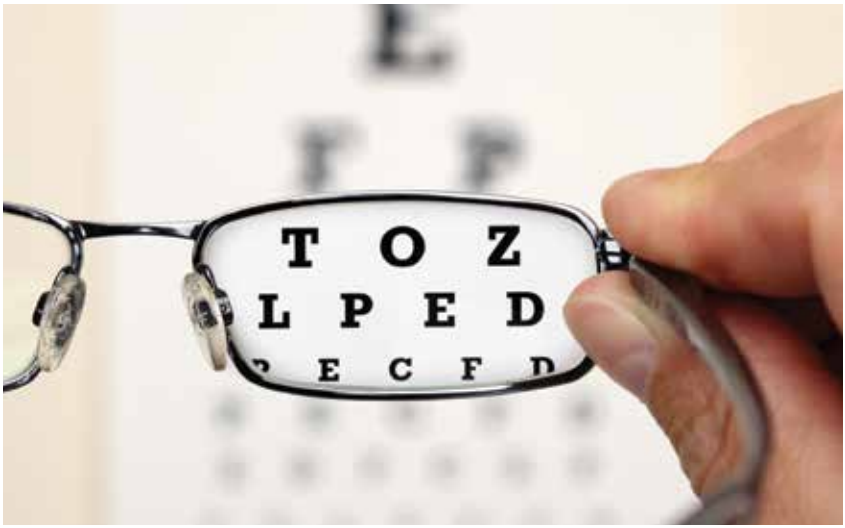


This process causes nerve conduction to slow or stop, leading to impaired vision, limb weakness or paralysis, and other symptoms common to NMO. Recent research suggests that myelin can be repaired and reversed, but only if the process of inflammation that caused the initial breakdown of myelin is arrested. This is why it is so important to recognize and diagnose NMO quickly and accurately, enabling treatment early in the course of disease that may minimize inflammation and demyelination.

Symptoms of Tissue Damage

Optic Neuritis

Optic neuritis (ON) is inflammation of optic nerves that shuttle visual information between the eyes and brain. In NMO, this process may involve one (unilateral ON) or both (bilateral ON) optic nerves. **Optic neuritis is**



the most common and often the first symptom in NMO. It is characterized by eye pain, vision loss and optic nerve dysfunction. Inflammation causes loss of vision usually because of swelling and injury of the myelin coated neurons in the optic nerves. The visual loss may be mild or severe, reversible or irreversible.

Transverse Myelitis

Inflammation across an extensive segment of the spinal cord is known as transverse myelitis (TM). The term **transverse** describes the position of inflammation along an extended length of the spinal cord. "Myelitis" refers to inflammation of the spinal cord. In NMO, TM

CIRCLES: AN NMO PATIENT STUDY

CIRCLES is the **C**ollaborative **I**nternational **R**esearch in **C**linical and **L**ongitudinal **E**xperience **S**tudy of NMO. Some of the goals include:

- Understand causes
- Improve diagnosis
- Address symptoms
- Prevent relapses
- Find cures

Blood samples and clinical data are vital for research in NMO. Many developments come from doctors and researchers analyzing blood samples and data.

If you or someone you know has been diagnosed with NMO, donating blood and clinical data to CIRCLES is a great way to contribute to the cure.

Learn more at:
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often extends to three or more spinal vertebrae in length (longitudinally extensive) over the spinal cord. The part of the spinal cord where the damage occurs determines which other parts of the body (e.g. limbs, bowel and bladder, etc.) may be affected.

- Nerves interacting with the **cervical** (neck) area of the spinal cord control signals to the neck, arms, hands and breathing muscles (diaphragm).

- Nerves interacting with the the **thoracic** (upper back) area of the spinal cord send signals to the torso and some parts of the arms.
- Nerves interacting with the **lumbar** (mid-back) area of the spinal cord control signals to the hips and legs.
- **Sacral** nerves interacting with the lowest segment of the spinal cord relay signals to the abdomen, groin, toes, and some parts of the legs.

Damage at one position of the spinal cord can affect function at and below that segment. **Pain in the lower back** is often a **symptom of TM.** By comparison, **demyelination usually occurs at the upper back thoracic level**, causing problems with leg movement, bowel and bladder control, skin numbness, tingling or pain.

Do you know?

NMO patients can join an email list or visit our Facebook and Twitter pages to receive information and learn the latest updates about NMO clinical trials.

See Sections 5 & 6 to find out more