



Understanding and Treating Multiple Sclerosis

By Amy Scanlin, MS

While research has greatly increased our understanding of what causes MS, much still needs to be learned. In the meantime, new treatments have been developed and many more are in the pipeline.

A lot more is known about multiple sclerosis (MS) today than a few years and even just a few months ago. In 1970, scientists knew of one gene linked to MS. In 2007, that number increased to three genetic links, and in early August 2011, scientists announced that there are 57 genetic links with the confirmation of 23 previously identified genes, 29 newly identified genetic variants and five genetic candidates worthy of further study. These are promising times for the 400,000 individuals in the U.S. and the 2.5 million worldwide who suffer from MS and its related symptoms!'



What Is MS?

MS is a chronic disease affecting the central nervous system that, in turn, prohibits the nerve cells in the brain from communicating with the spinal cord. When the protective fatty myelin sheaths surrounding the axons of the brain and spinal cord are damaged or scarred (demyelination), the result is a reduced ability to perform everyday activities, reduced cognitive function, impaired or lost vision, and even loss of bladder control and paralysis. The term multiple sclerosis refers to the numerous lesions, or scleroses, that form when the nervous system is attacked.

MS attacks more women than men, and it is typically diagnosed between the ages of 20 and 40, although it can be seen at any age. It is more common in Caucasians than African-Americans, but those men and African-Americans who do have MS tend to have more severe attacks. The incidence of MS is higher in persons who have a close relative with the disease, and if it is a first-degree relative, there is a 12- to 20-fold increase in risk.² The rate of MS also is higher in those who spent formative years farther

from the equator, where there is less sunlight. Interestingly, children who are born in one area and migrate to another prior to age 15 are thought to take on the risks of MS of their newly adopted area.² So, if a child is born closer to the equator and then moves farther away, they take on the same risks for MS as the population of the area to which they moved.

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To be diagnosed with MS, doctors must confirm two separate incidences of demyelinations, or lesions, in the white matter; two or more remissions of neurological deficits; and have the diagnosis confirmed by an MRI. Doctors also look for “increased IgG synthesis with positive oligoclonal bands (OCBs) in the spinal fluid.”²

Some people with MS can live for years without symptoms, while others become disabled rather quickly. It is a disease whose progression is difficult to predict.

Causes of MS

The latest study in which 57 genetic links to MS were identified was a major breakthrough for scientists who for years have been looking at a variety of possible theories on the causes of MS — from the controversial Italian researcher Dr. Paolo Zamboni’s theory of blocked veins, to more widespread theories of immunologic causes.

Now, scientists can say that about 80 percent of the 57 genes identified that are associated with MS are immunologic and that inflammation of the immune system triggers MS attacks. Although scientists don’t think MS is a hereditary disease, they know that it is a function of one’s genes, perhaps interacting with environmental factors, and perhaps also in conjunction with a vitamin D deficiency, which can cause the immune system to attack the nervous system.

Many of these newly identified genes also are involved in the functioning of T cells, which attack foreign invaders, and about one-third of them are associated with other autoimmune disorders such as Crohn’s disease and type 1

diabetes,³ two conditions often found in those with MS. Yet, even with so much information starting to come together, scientists think that these new gene variants may still account for only a small portion of the big picture. The rest is yet to be discovered.

Symptoms and Subtypes of MS

Symptoms of MS can occur as discrete attacks or as a relapsing form, or the symptoms can accumulate over time, as with progressive MS. Symptoms also may completely disappear between attacks, but the underlying effects during those attacks are the cause of the neurological problems that later occur.

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The majority of MS patients have the relapse-remitting form, potentially with long periods between symptoms and no indication that a relapse is about to occur. After a relapse, any deficits suffered can disappear or remain, compounding over time with each subsequent relapse. A typical number of attacks with relapse-remitting MS is one to two per year.⁴

Many patients initially diagnosed with a relapse-remitting form of MS develop secondary progressive MS. These patients begin to have a neurological decline between attacks without any periods of remission. The typical time for developing secondary progressive MS is less than 20 years, and in women, this development happens around the time of menopause.⁵

Those with primary progressive MS never go into remission after the first onset of symptoms, and this subtype is usually diagnosed at about the age of 40. The least common subtype of MS is progressive relapsing, and these patients have a steady neurological decline once symptoms begin, as well as clear attacks.

Treatment for MS

Developing treatments for MS is expensive, averaging about \$1 billion to bring a drug to market at an annual treatment cost of between \$40,000 and \$50,000. Today's treatments for MS include attempts to lessen the progression and long-term impacts of the disease, as well as to reduce the number of flare-ups and attacks.

One of the top 10 medical breakthroughs in 2010, voted on by the Cleveland Clinic, was Gilenya capsules (manufactured by Novartis International AG). Gilenya was approved as the first oral treatment for MS by the U.S. Food and Drug Administration (FDA) for reducing the number of relapses, as well as for reducing the physical symptoms of MS.⁶ Another drug recently approved by the FDA is Ampyra (manufactured by Acorda Therapeutics). Ampyra has been shown effective as the first treatment to target the symptoms that severely compromise MS patients' ability to walk, and it has shown to be effective for those with all types of MS.

Two more promising drugs are predicted to come to market in 2012. Sanofi and its subsidiary Genzyme are developing alemtuzumab (Campath) with Bayer HealthCare. The monoclonal antibody is already used to treat leukemia, or T-cell lymphoma, and it also is used in conditioning regimens for bone marrow or kidney transplantations. Results from the Phase III clinical trial show a 55 percent reduction in relapse at two years in adults with relapsing-remitting MS treated with alemtuzumab. The companies expect to file for United States and European Union approval of the drug for MS in early 2012. They have already been granted a fast-track designation by the FDA.⁷

The second promising drug is BG-12 (BG00012, dimethyl fumarate) from Biogen Idec, which is an investigational oral therapy in Phase III clinical development as a monotherapy for the treatment of relapsing-remitting MS, and in Phase II clinical development for rheumatoid arthritis. BG-12 received fast track designation in MS from the FDA, which may expedite U.S. regulatory review.⁸

Other methods of treatment for MS include powerful autoimmune-suppressing corticosteroids administered intravenously over the course of a few weeks to help lessen the risk of long-term damage of attacks.⁴ While many doctors and patients feel this type of therapy is effective, some studies have shown little to no long-term difference between control and study groups. More research is needed to determine whether corticosteroids actually work.

The American Academy of Neurology recommends physicians consider the blood-cleansing procedure of plasma exchange (plasmapheresis) on a short-term basis as a secondary therapy for those with rapidly progressing MS who are unresponsive to corticosteroids.⁹ This therapy has not shown to be effective for those with secondary or primary progressive MS; however, it has shown to be successful to treat other immune disorders.

Other therapies such as IVIG or Mitoxantrone often are used as secondary treatments for those patients with long periods of clinical remission. In fact, several published European studies have confirmed the benefits of IVIG therapy in those patients with clinically definite relapsing-remitting multiple sclerosis. These studies demonstrated a reduction in the acute relapse rate and the number of contrast-enhanced lesions on monthly MRI scans. Most importantly, the patients receiving multiple sclerosis treatments in the form of IVIG therapy spent significantly more time in an improved or stable neurological state as compared with the placebo groups, suggesting a better quality of life for the IVIG patients during remission.¹⁰

Managing Day to Day

While many years ago it was advised that patients with MS not do any form of exercise for fear of exacerbating painful symptoms, today that is not the case. Patients working closely with a doctor and physical therapist can develop appropriate programs that show promise in not only reducing symptoms of MS but improving cardiovascular function and strength, bone density, bowel health, mood and overall quality of life.

Aerobic exercise has a positive effect on the parts of the brain most affected with MS, including fewer and smaller lesions and improved cognitive capacity, as evidenced by higher scores on cognitive testing.¹¹ Researchers also have found that fitter MS patients have more gray matter, or cell bodies, in the brain, as well as less deterioration of white matter, or fibers that connect the gray matter areas, which are both significant to the brain's ability to process information.

In addition, mindful meditation can help manage depressive feelings and fatigue. A study conducted in Switzerland of those with both relapse-remitting and secondary progressive MS found that patients can see great emotional benefits from a mind-body connection.¹²

Before getting started with a fitness program, patients should speak to a doctor to determine what programs might be appropriate. They should be especially careful to



avoid tripping and slipping hazards by having a bar or steady object close by. And, they should avoid becoming overheated, as many with MS feel symptoms are greatly exacerbated when the body temperature rises. For these reasons, water exercise is a particularly popular choice, provided there are non-skid surfaces in the locker room and along the pathway to the pool.

Also popular are yoga and tai chi, gentle strength training protocols, and both arm ergometers and bicycles. Again, any exercise program should only be undertaken with doctor supervision and modified as needed.

Future Outlook

As more genes are identified and researchers learn more about the role the immune system plays in the development of MS, patients can expect more personalized treatments while researchers look at new opportunities for drug development. There are numerous trials under way in the treatment of MS, and many are showing promise.

In the prevention of relapse, one Phase II trial found that a liquid injectable form of the monoclonal antibody daclizumab reduced the rate of recurrence.¹³ There also are positive indications that alemtuzumab, an intravenous therapy delivered over two years, five days a week for the first year and three days per week in the subsequent year, may be a new therapy

worthy of further exploration after a Phase III study revealed a 55 percent reduction in relapse rate.¹⁴ The FDA has designated alemtuzumab a “fast track product.”

In order to prevent MS and better treat its symptoms, scientists need a better understanding of the role inflammation plays on its progression, the role of environmental interactions, as well as the specific molecules involved in attacks. One consideration of an environmental interaction is how tobacco smoking interacts with the presence of the Epstein-Barr (EB) virus. Those with a history of multiple mononucleosis attacks caused by the EB virus or who have higher levels of the virus’ antibodies in the blood and who have a history of smoking are nine times more likely to develop MS than those without the EB gene.¹⁵

Another environmental consideration is how vitamin D, gained from sunlight exposure, has shown to be an important factor in the prevention of MS. Alterations of genes in both vitamin D hormone receptors and synthesis have been associated with increased instances of MS, especially in combination with estrogen, which along with vitamin D prevents inflammation of the central nervous

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system. When women enter puberty, they become more dependent on estrogen for the autoimmunity protection of vitamin D. As women produce less estrogen in menopause, their ability to use vitamin D decreases and their MS risk factors increase. This is the time when doctors see progression from relapse-remitting to secondary progressive forms of MS. Scientists are looking at the possible links of estrogen replacement and vitamin D supplements to prevent that transition.⁵

The good news is that progress is being made in new therapy and treatment trials, which are providing more and more information each day. In the meantime, the Multiple Sclerosis Society offers links to online social networking communities where patients who have been diagnosed can share their stories. Visit www.nationalmssociety.org/online-community to learn more.

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