Recent research, funded by the National MS Society, shows nearly one million people are living with MS in the United States, more than twice the last reported estimate. This new information further highlights the importance of MS research to better understand its causes and symptoms, develop more effective treatments, and ultimately find its cure. MS symptoms vary a great deal from one person to another. For MS Awareness Month, our March newsletter focuses on some of the disease’s most impactful symptoms. Many people with MS struggle with their thought processes at some point in the course of the disease. Some notice problems with their memory. Others find they have trouble doing more than one thing at a time, or they take longer to process information. Some people find they have problems learning new tasks, while others may struggle with organization, planning or prioritizing. Our first article covers the cognitive effects of MS, which often represent its greatest challenges.

According to the National MS Society, 80% of people with MS experience fatigue, and over half rank it as one of their most troubling symptoms. MS fatigue is complex, with many layers and contributing factors. In some cases fatigue is “secondary” to an underlying cause and may be effectively addressed by treating the source. Beneath these secondary causes is “primary” MS fatigue, the cause of which is unknown and a major focus in MS research. Learn more about MS fatigue and what can be done to keep it to a minimum.

Studies show more than half of people living with MS have difficulty sleeping. This could be for a variety of reasons. No matter what the cause, sleep deprivation has the potential to not only aggravate physical MS symptoms, such as balance and spasticity, but can also worsen things like cognition and fatigue. Awareness and treatment of sleep disorders is vital for improving the health and quality of life for people living with MS. Fortunately, there are many options to help in this regard, including both behavioral and pharmaceutical remedies. Read more about the importance of a good night’s sleep in people with MS.
The 2019 ACTRIMS Forum took place in Dallas, TX, at the end of February. Approximately 1,100 attendees met to discuss the latest knowledge gained from cutting edge MS research, as well as clinical approaches for MS diagnosis and management. ACP’s Director of Alliances and Collaborations, David Gwynne, was in attendance and shares one of the highlights from the conference. Our Repository Spotlight focuses on four posters presented at ACTRIMS by researchers from the Neuroimmunological Disorders Gene-Environment Epidemiology Laboratory at Case Western Reserve University. Each poster summarized data from a groundbreaking study using ACP Repository samples and data.

Our iConquerMS Spotlight highlights REAL MS. The most recent round of surveys was released in March. If you haven’t already done so, please complete yours today! If you aren’t already a member of iConquerMS, please consider joining this powerful network. Our goal is to provide researchers with the most accurate representation of the entire MS population possible. Maximizing enrollment and participation in REAL MS will result in a clearer picture of what living with MS is really like. Every piece of data expands the pool of information that researchers can draw from.

Lindsey Santiago wears many hats at home and at work. As Development Associate for ACP, she plays a fundamental role helping with such things as the newsletter, third party fundraisers and website updates. At home, she enjoys spending time with her family and juggling all that is involved in taking care of her 3-year old son. It’s our pleasure to share with you a recent article from Yahoo Lifestyle, featuring Lindsey and her family. In the article, Lindsey shares about her MS journey and what it’s like to parent living with the disease.

We hope you enjoy our newsletter and encourage you to share it with anyone you think may be interested in learning more about ACP.

Jan and Lindsey, on behalf of the Accelerated Cure Project Team

**MS and Your Mind**

When people think about MS, they may not associate it with cognitive difficulties, even though up to 65 percent of people with MS struggle with their thought processes at some point in the course of the disease. Some notice problems with their memory, particularly finding words or remembering events from the past. Others find they have trouble doing more than one thing at a time (multitasking), or they take longer to process information. Some people find they have problems learning new tasks, while others may struggle with organization, planning or prioritizing. For many, the cognitive effects of the MS represent its greatest challenges.

The medical term used to describe this loss of mental function is cognitive impairment. While cognitive changes are more common later in the course of the disease, they can occur at any time (even as the first symptom of MS)
and can vary considerably from person to person. Like the physical symptoms of MS, cognitive changes are likely to progress over time. They may worsen during an exacerbation and then improve afterwards. However, once changes in mental function occur, they rarely disappear completely. Overt dementia in MS is rare. Often a few specific abilities are affected while others are spared. Interestingly, cognitive functions that are generally preserved in MS include general intellect, long-term memory, conversational skills, and reading comprehension. The severity and frequency of cognitive symptoms may fluctuate, ranging from intermittent episodes to more pervasive changes, which can significantly impact a person’s daily life. The degree of cognitive dysfunction does not appear to be related to the amount of physical disability a person with MS may have. Individuals with little or no physical impairment can experience significant cognitive changes while those with severe physical disability may have very little or no cognitive impairment.

Cognitive dysfunction substantially impacts the lives of those with MS and their families, in some cases enough to interfere with work. Studies show half to three-quarters of people with MS are unemployed within 10 years of diagnosis and cognitive impairment is one of the leading causes of unemployment. Those with impaired cognition tend to participate in social activities less frequently and isolation is not uncommon. Cognitive dysfunction may also place significant additional strain on an individual’s caregiver, who must help their loved one deal with its ramifications. In very rare instances, cognitive dysfunction may become so severe that the person with MS can no longer function independently.

Cognitive dysfunction in MS is primarily the result of changes in the brain due to progressive damage to the protective coating of nerve cells (called the myelin sheath) and the formation of lesions throughout parts of the central nervous system. Research is ongoing to identify the specific areas of the brain that may play a role in cognitive impairment with MS. The hope is that through such studies, treatments may eventually be designed to target these areas and minimize or prevent any effects that MS may have on mental function. In addition, the disease can cause atrophy, or shrinkage, in certain parts of the brain and spinal cord. Some studies suggest brain atrophy contributes to cognitive impairment. Because MS can affect any part of the brain, almost any cognitive function can be impaired.

Cognitive changes in MS are measured in a variety of ways. A full neuropsychological evaluation, which involves multiple tests to measure memory, attention and many other parts of cognition, provides the most comprehensive information about the kinds of problems with thinking that may exist and whether they may be due to MS or some other complicating factor. Neuroimaging (MRI scanning) is frequently used to determine what specific areas of the brain may be affected and causing cognitive problems. In general, cognitive function correlates with the number of lesions on MRI, as well as the degree of brain atrophy. Research studies often use a test called the Paced Auditory Serial Addition Test (PASAT) to assess cognitive function, specifically auditory information processing speed and flexibility, as well as calculation ability. Single numbers are presented via an audio recording every two or three seconds and the person must add each new digit to the one immediately prior to it. The score for the PASAT is the total number correct out of 60 possible answers. Another commonly used
assessment in research is the Symbol Digit Modalities Test (SDMT). Participants in this test are given a reference key that they must use to help them associate numbers to a series of geometric shapes. The SDMT is scored based on the number of correct substitutions within a 90 second period. For both tests, higher scores indicate less cognitive dysfunction.

Although there is no way to predict whether or not an individual will develop MS-related cognitive impairment, there are a number of risk factors involved. Research shows that people with progressive forms of MS experience more cognitive decline than those with relapsing remitting MS (RRMS). Earlier onset of MS increases one’s chance of developing MS-related cognitive decline. Race also plays a role in the impact of MS on cognition. African-American patients with MS develop cognitive deficits earlier in the disease course compared to Caucasian patients. However, African Americans also tend to have a more aggressive disease course and the cognitive findings may be a result of that. Studies show gender is another risk factor for cognitive impairment in MS, with the incidence and severity of cognitive deficits being higher in men than women. Intelligence and education also play a role in the likelihood of cognitive decline not only in people with MS, but in the general population. According to the cognitive reserve theory, the more you use your brain, the greater your chances of avoiding symptoms of cognitive impairment. A study following patients with MS over a five-year period showed that those with a high cognitive reserve at baseline experienced no loss of cognitive function, while those who started with a low cognitive reserve suffered significant cognitive decline.

There are many factors that can interfere with thinking and, as a result, may further impair mental processes. In cases like this, cognitive function may improve with treatment of the underlying exacerbating factor. In general, those who drink alcohol excessively or who use drugs may have altered thinking. People with sleep disorders may experience cognitive problems related to sleep deprivation. Individuals with some medical conditions, such as low thyroid, may also have problems with memory. A recent study reported heavy smokers with MS have increased cognitive impairment when compared to nonsmokers. Research has also revealed a significant association between depression in MS and cognitive dysfunction. In addition, many medications used to treat MS and its symptoms can cause problems with thinking, such as steroids, muscle relaxants and some antidepressants. It’s important to discuss your medications with your healthcare team to see if one or more of them could be causing cognitive problems and, if so, to see if they can be reduced or stopped, or if there are alternative treatments that can be used.

Researchers are working to identify treatments that may stabilize, or improve, cognitive dysfunction in MS. A number of commonly used MS disease modifying medications are thought to be of benefit. A 2012 study showed that early treatment with Betaseron provides sustained benefit with regards to mental function in MS. A 2014 study showed Avonex and Rebif are also helpful in this regard. A study published in 2018 showed individuals treated with Tysabri (natalizumab) demonstrated significant improvement in mental function over 2 years of treatment. Italian researchers reported the same benefit from Tysabri treatment over a 3-year period. Other agents have also been evaluated for their ability to treat cognitive impairment in MS. One study recently
evaluated four drugs (ginkgo biloba, donepezil, rivastigmine, and memantine) in people with MS in large-scale, double blind, placebo-controlled clinical studies. Unfortunately, none of these compounds demonstrated beneficial, reproducible improvements in mental function.

Cognitive rehabilitation therapy is the process of relearning cognitive skills that have been lost or altered as a result of damage to the brain. This type of treatment centers on the concept that practicing a specific cognitive task strengthens the communication between neurons required for that task. If skills cannot be relearned, then new ones have to be taught to enable the person to compensate for their lost cognitive function. Results from trials focusing on cognitive rehabilitation in MS are mixed. A recent study showed that, while cognitive rehabilitation therapy may not be of direct benefit, it does help alleviate fatigue in people with MS and this may, in turn, help improve cognitive function.

There is evidence that physical activity may improve cognitive function in people with MS. A 2010 study shows yoga may reduce fatigue and improve attention in people with MS. Data presented at the 2016 ACTRIMS Forum suggest that treadmill walking has beneficial effects on inhibitory control (the ability to focus on relevant stimuli and ignore irrelevant ones) in people with MS who can walk. Other research indicates physical activity may improve cognitive processing speed, but not learning and memory. While definite conclusions cannot be drawn from these studies, the positive association between physical activity and cognitive function suggests that exercise might be an effective non-drug treatment for cognitive impairment in MS.

While cognitive difficulties may be challenging at times, there are many strategies that may help. However, it’s important to note that those struggling with cognitive difficulties should first consult with their physician. Mental or emotional changes may be symptoms of depression, which is not only common in people with MS, but may be easily treated. A 2010 study found that people with MS are unlikely to use coping strategies. Instead, many avoid situations in which their cognitive impairment might be evident or obvious to others. It’s important to have a support system in place, rather than coping alone. Sharing these concerns with others may offer reassurance to those living with MS that they are not alone in their experiences. There are also a number of preventive measures that may be helpful. The brain benefits from mental exercise in the same way the body benefits from physical exercise. The more individuals challenge their brain with things like mental math, memory games or puzzles, the more likely they are to retain certain mental functions. Getting enough sleep is also crucial to optimize mental functioning. Avoiding mental stimulation before bedtime and maintaining the same sleep schedule every day may be helpful. Some people with MS find that planning their day so the most challenging tasks are at a time of day when they feel sharpest to be of benefit. Those having difficulty concentrating may also find it helpful to take a break and refresh before continuing in their task.
One of the best methods for improving memory is to take notes wherever and whenever information needs to be recalled. Keeping notes organized in a central place, along with other important things like bills and other mail, keys, purses/wallets or shopping lists may be helpful. Using things like calendars, checklists and alarms for reminders about things like taking medications or appointments may also be of benefit. Many find repeating what they hear and verifying it is correct, or repeating the information at intervals spread out over time will improve their ability to remember it. Others build associations to help their memory. Combining different modes of learning to reinforce the same information may also help with information retrieval. In other words, an individual may be more likely to remember something if they “see it, say it, hear it, write it, and do it.”

An important strategy for improving attention is to reduce or eliminate distractions. Sometimes people have thoughts that interfere with attention to the matter at hand. With this type of distraction, a good plan is to write down any ideas that might be monopolizing one’s thoughts and try to set them aside to focus on at a later time. Many find doing one thing at a time is helpful in keeping their attention on the task at hand. Avoid switching back and forth from one topic or task to another.

MS is a complex disease with many psychological aspects. It is important for people living with MS to understand and address these changes along with the physical ones. Cognitive changes can have a significant impact on a person’s ability to work and fulfill family responsibilities. Family members may not realize that MS can cause cognitive problems and this misunderstanding can result in stress and hard feelings. Research is ongoing to understand the underlying mechanisms and causes of cognitive decline in MS in hopes of discovering new therapeutic targets. In the meantime, employing a number of strategies to increase attention and memory can help people with MS and their families minimize its effect in their day-to-day lives.

**Understanding and Living With MS Fatigue**

According to the National MS Society, 80% of people with MS experience fatigue, and over half rank it as one of their most troubling symptoms. Nearly everyone feels overtired or overworked from time to time and such instances of languor usually have an identifiable cause and a likely remedy, such as a good night’s sleep. Fatigue is an unrelenting exhaustion that lasts longer, is more intense and isn’t relieved by rest. It’s a nearly constant state of weariness that develops over time. Fatigue can be either physical or cognitive, or both at the same time. Physical fatigue may affect an individual’s energy and motivation. Limbs may feel heavy and hard to use, as a result individuals may feel the need to lie down immediately.
Cognitive fatigue, on the other hand, could affect one’s concentration. Individuals with cognitive fatigue may have difficulty following a conversation or thinking of words or numbers. In either case, fatigue negatively impacts the functioning and quality of life of the majority of people living with MS.

MS fatigue is complex, with many layers and contributing factors. In some cases fatigue is “secondary” to an underlying cause and may be effectively addressed by treating the source. For example, many people with MS struggle with depression. Depression itself can manifest with fatigue, so it is often difficult to distinguish between the two. In addition, other symptoms of depression, such as lack of motivation, are often mistaken for fatigue. Research shows a direct association between fatigue and depression, even considering the overlap between the two conditions. In instances where depression and fatigue occur concurrently, fatigue may be effectively addressed by treating the underlying depression. Investigators also found a direct relationship between fatigue and disease severity (subjects with more disability were more likely to experience fatigue). In addition, subjects with progressive MS appeared to have higher fatigue scores (experience more fatigue) than those with RRMS. However, this difference may be attributable to the differences in disability among the types of MS. By the same token, people with MS may have sleep disorders that interfere with restful sleep. In fact, researchers at the University of Washington found the prevalence of sleep problems in people with MS is significantly higher than in the general population, particularly in women living with the disease. Exhaustion from a lack of restful sleep is considered to be a contributing, if not a causative, factor in MS fatigue. Medications used to treat MS and its symptoms have the potential to cause fatigue. For example, fatigue is a side effect of some disease modifying treatments, including interferons (Avonex, Betaseron and Rebif), Tysabri and Novantrone. Drugs taken for MS symptoms like spasticity (baclofen or diazepam) or nerve pain (gabapentin), to name a few, can also contribute to fatigue. In some cases, a medication adjustment can help with fatigue, however anyone considering such a change should first consult with their healthcare team. Sometimes, people with MS have other medical conditions, such as infections, anemia, or thyroid conditions, which can also increase fatigue.

Beneath these secondary causes is “primary” MS fatigue, called lassitude, the cause of which is unknown. Lassitude has a number of specific characteristics that help distinguish it from secondary MS fatigue. Lassitude generally occurs on a daily basis. It is considered more severe than secondary MS fatigue, and is more likely to interfere with daily responsibilities. Lassitude often occurs early in the morning, even after a restful night’s sleep. This type of fatigue comes on easily and suddenly, tends to worsen as the day progresses and is often aggravated by heat and humidity. No matter what form of fatigue an individual with MS may experience, this overwhelming tiredness can affect anyone with MS, regardless of physical disability, and occur at any time in the course of the disease. Even though it is more likely in those with higher levels of disability, it is not always the case. Fatigue can also be the most prominent symptom in a person who otherwise has minimal physical limitations. People with MS may also find that fatigue worsens their other MS symptoms.

The exact cause of MS-related fatigue is still unknown. However, researchers are working to figure out this mystery. There is evidence that fatigue is related to the general activation of the immune system.
that occurs in MS. As discussed in our January 2019 newsletter, cytokines are chemical messengers that are secreted by certain cells in the immune system. Researchers in Germany found pro-inflammatory cytokines are significantly higher in MS subjects with fatigue, compared to MS subjects not experiencing fatigue. This suggests that fatigue is at least partially mediated through activation of these cytokines. Another study showed that the levels of the hormone dehydroepiandrosterone (DHEA) are lower in MS subjects with sustained fatigue when compared to those without fatigue, suggesting the endocrine system may play a role. The fact that many people with MS report increased energy while taking corticosteroids as treatment for their neurologic symptoms further supports a possible hormonal influence. However, it’s important to note that, because of the chronic nature of fatigue and risks of long-term steroid use, steroids are not recommended as treatment for fatigue. Other studies suggest that MS fatigue stems from damage to the central nervous system caused by demyelination. Specifically, one study suggests a reduced transmission of electrical signals in the brain could play a role and another study points to nerve loss as a contributing factor.

In some cases drugs may be used in treating fatigue. However, medication is not a solution to fatigue on its own. Because different factors can cause or add to MS-related fatigue (such as depression or sleep disorders), anti-fatigue medications should be used in conjunction with treatment for these factors (when applicable). It’s also important for people with MS to see their physician regularly to ensure their disease is under the best control possible. Modafinil (Provigil) is a medication used to increase wakefulness in individuals with the sleep disorder, narcolepsy. It is used off-label in MS to treat fatigue and sleepiness. Studies suggest that low dose modafinil (200 mg daily) significantly improves both, and is well tolerated in people with MS. Armodafinil (Nuvigil) is a medication that is similar to modafinil and is also prescribed for the treatment of MS fatigue. Amantadine (Symmetrel) is an antiviral medication used in Parkinson’s disease. It has also been used in the treatment of MS fatigue since the 1980s, although its benefit in this regard is not well documented. Methylphenidate (Ritalin) is a central nervous system stimulant used for treatment of attention deficit disorders. In some cases, it is also helpful in reducing MS fatigue. Studies are underway to confirm this benefit. Dextroamphetamine (Dexedrine) is also a stimulant medication. Its effects on MS fatigue are similar to those of methylphenidate. A recent study suggests that aspirin may lessen fatigue in people with MS (among other benefits). While aspirin usage is relatively common in the general population, its use by people with MS also has the potential for negative effects on specific components of MS disease process (for example, further decreasing mitochondrial function, which is a cause of nerve degeneration MS). Further studies are needed to confirm the potential benefits, as well as the risks, of aspirin treatment for people with MS.

A number of alternative therapies may provide some benefit for MS-related fatigue. Some people with MS find that caffeine (in moderation) can be helpful in managing fatigue. Unfortunately, caffeine is an irritant to the bladder, and can exacerbate urgency and frequency. Individuals with MS should speak with their healthcare team about their caffeine intake to be sure they are not exceeding levels that are appropriate for them. Acetyl-L-carnitine (ALCAR) is a dietary supplement that appears to reduce MS-related fatigue, however research to support this benefit is mixed. A small study of 36 subjects, done in 2004, suggests ALCAR is well tolerated and more effective than amantadine for the treatment
of MS-related fatigue. Other studies claim there is insufficient evidence to support this benefit. As discussed in our February 2019 newsletter, some herbs are used to help relieve fatigue. These include ginkgo biloba, valerian, St. John’s wort, as well as Siberian and Asian ginseng. As we mentioned last month, many of these herbs have problematic side effects that should be carefully considered before use. Some people with MS turn to Tai chi and yoga for relief of their MS fatigue. A recent review of studies conducted on Tai chi practice and MS concluded the evidence to support a benefit with regard to improving fatigue is inconclusive. However, researchers found Tai chi significantly improves quality of life and functional balance in people with MS.

While proper treatment can help control fatigue, changes in lifestyle can also prove beneficial. Strategies to conserve energy are often helpful. An analogy can be made for people with MS between bank accounts and energy levels. Both benefit from the same rule of thumb – less money, or energy, used now means more will be available later on. In other words, doing too much early in the day can burn through all energy stores and leave an individual feeling tapped out. Energy rationing is especially important for people with MS, who tend to start the day with lower energy levels than the average person. For some, a brief rest is very helpful to recharge and scheduling breaks (alternated with periods of activity) is useful to avoid becoming too tired too quickly. If a task is too much to handle at one time, it may be helpful to divide it into smaller parts, or ask for help if this isn’t possible. Planning one’s activities can also help, for example to avoid going up and down the stairs more often than necessary. Listing activities in their order of importance can be useful to see what needs to done first and what can wait until another day, should all energy be used up before reaching the end of the list. Those with limited energy often need to accept the fact that not everything will necessarily be completed when and how one prefers them to be done.

Efficiency while performing household duties is also useful in battling fatigue. Whenever possible (when cooking or cleaning, for example), arrange supplies in advance to minimize the amount of time spent standing. With respect to meals, selecting menus in advance with easy recipes can help preserve stamina. Having food delivered (rather than shopping) is the most time and energy efficient option. If that’s not an option, make a list of all necessary ingredients for the week’s meals before shopping for food. Being familiar with a local store and the aisles where individual items are located can assist with saving time and energy as well. Whenever possible, prepare double portions of a meal and freeze leftovers for another day. This provides extra meals that require little time to prepare.

It’s important for people with MS to recognize and avoid environmental factors that may cause fatigue. For example, many find it helpful to avoid extremes in heat (long, hot showers or baths, for example) because it drains their energy. On a hot summer day, it may be useful to cool down with a fan or spray bottle, or stay in air-conditioning when possible. As mentioned in our May 2018 newsletter, the Multiple Sclerosis Association of America’s Cooling Distribution Program offers cooling vests, smaller products to wear under clothing and other accessories to help people with MS keep cool.
Other basic principles of healthy living can also be helpful in managing MS fatigue. Eating a well-balanced, healthy diet can help boost energy levels. Decreased physical activity can lead to tiredness and lack of energy. Regular, moderate exercise can decrease these feelings, as well as improve strength and foster a more positive attitude. Any person with MS who is considering a new exercise program should consult with a physician before starting, and throughout, their regimen. An exercise program needs to fit the capabilities and limitations of the individual and it may need to be adjusted as changes in MS symptoms occur. Periods of exercise should be carefully timed to avoid the hotter periods of the day. Many people with MS find exercising in water to provide exceptional benefits as it is not only cool, but water helps them move in ways they may not be able to on land. Finally, managing stress can play an important role in combating fatigue. This can be done in a variety of ways. Adjusting expectations and limiting daily to-do lists will likely bring a sense of accomplishment that can go a long way toward reducing stress. Educating family and friends about MS fatigue may also help. Given that fatigue is an “invisible symptom” of MS, they might not understand it and may be more helpful if they appreciate its full impact. Some people with MS find support groups to be a source of comfort and camaraderie, as well. Others rely on relaxation techniques to help reduce stress.

Fatigue management has many dimensions and often requires a team effort between family, caregivers, healthcare providers, and many other members. Physicians and other healthcare providers can prescribe and monitor medications, as well as provide education and help develop strategies. Family and caregivers can help provide for physical needs, or with moral support. Perhaps more than with any other symptom of MS, the key player in coping with fatigue is the person with MS. He or she has the ultimate responsibility for implementing any suggested game plan, and making adjustments based on its effectiveness. Managing fatigue involves both trying to keep energy levels up and using energy efficiently. Finding the right balance may be a learning process that requires trial and error. As an individual with MS goes through this process, it’s important for them to have a support system (team) to lift them up when they may falter. Through this team effort, it’s possible for individuals with MS to function, participate in extracurricular activities and have the best quality of life possible.
The Elusive Forty Winks

According to the Irish proverb, “a good laugh and a long sleep are the two best cures for anything.” Both points certainly ring true. Regardless of one’s circumstances, maintaining a sense of humor is something to strive for. Unfortunately, a good night’s sleep can be much more fleeting. Studies show more than half of people living with MS have difficulty sleeping. This could be for a variety of reasons. Some may have to get up to use the bathroom frequently at night, while leg spasms or pain may awaken others. Some may be taking medications that cause insomnia. No matter what the cause, sleep deprivation can not only aggravate physical MS symptoms, such as balance and spasticity, but it can also worsen things like cognition and fatigue, which are harder to see, but equally disabling.

Sleep disturbance is a general term for a wide range of sleep-related symptoms and disorders. While people with MS may experience any (or multiple) of these conditions, there are several that they are more prone to. A 2014 study from the University of California Davis (UC Davis) reported that 32% of people with MS experience moderate to severe insomnia. Insomnia is characterized by difficulty initiating or maintaining sleep. Some of the most common MS symptoms, such as pain, bladder dysfunction, spasticity, overheating, stress, anxiety and depression, all have the potential to interfere with an individual’s ability to fall, or stay, asleep. Mobility issues may make it more difficult to shift positions in bed. The resulting discomfort from this can keep some people with MS awake. UC Davis researchers also found that 38% of people with MS have difficulty with obstructive sleep apnea. Interestingly, overweight individuals are also more prone to this disorder. This type of sleep-disordered breathing (SDB) occurs when a person’s throat muscles relax too much and their airway is temporarily blocked. While people with sleep apnea usually do not have trouble falling asleep, their breathing is affected once asleep, and the sudden inability to take a breath wakes them repeatedly throughout the night. There is evidence that people with progressive forms of MS and those with more severe disability are more likely to develop SDB. The above-mentioned study also showed that 37% of people with MS experience restless legs syndrome. Restless legs syndrome (RLS), also known as Willis-Ekbom Disease, is defined as a “neurologic disorder that is characterized by an overwhelming urge to move the legs when they are at rest.” According to the National Sleep Foundation, this urge is usually, but not always, accompanied by unpleasant sensations. In fact, several common MS symptoms, such as cramping, pain or spasticity, can be difficult to discern from RLS. The process underlying this condition is still poorly understood. It typically occurs in the evening or before bedtime, and is relieved by movement. Treatment involves medications, such as Requip (ropinirole). Reducing consumption of alcohol, caffeine, or nicotine can also be helpful. Other useful strategies include stretching, massaging, or applying hot (or cool) packs to the affected limb. There is evidence that certain medications can cause or worsen RLS. Other sleep disorders that are less common in people with MS include hypersomnia (difficulty with too much sleep), narcolepsy (uncontrollable lapses into sleep), or abnormal behaviors during sleep (such as acting out dreams). Individuals who think they may have a sleep disorder should consult with their healthcare team to identify any causative/contributing factors, and identify the best course of treatment.
Sleep disturbance is a known side effect of some medications commonly used to treat MS and its symptoms. For example, insomnia has been reported as a potential side effect of Lemtrada (alemtuzumab), an infusion therapy for RRMS. Insomnia and excessive daytime sleepiness are common side effects of steroids (which are frequently used to treat MS flares). Fortunately, the sleep disturbance from steroid use is temporary and usually resolves once treatment is finished. As mentioned in the article entitled “Understanding and Living With MS Fatigue,” stimulant medications such as modafinil, amantadine and methylphenidate are often prescribed to treat MS-related fatigue. Stimulants can cause restlessness and disrupt sleep. Fortunately, adjusting the dosage and timing of administration can help mitigate these side effects.

There are many tools available to help diagnose sleep disorders. It’s important to note that anyone having difficulty sleeping should have a physical examination to rule out any underlying medical causes before undergoing such an evaluation. Sleep logs (or diaries) are used to record valuable information related to an individual’s sleep habits and history. These diaries are typically completed by individuals on a daily basis over a period of several months, and include such information as estimated time to fall asleep, quality of sleep, number of awakenings, wake-up time and medication use. This information can be very useful to a diagnosing physician. A sleep study, or polysomnogram (PSG), is a test that records specific physical activities, such as brain waves, heart rate, breathing rate, eye movement, muscle activity, and blood oxygen levels during sleep. These data are then analyzed to determine a diagnosis. There are different types of sleep study. The Multiple Sleep Latency Test (MSLT), or nap study, measures the tendency to fall asleep, while your brain waves, chin-muscle activity, and eye movements are recorded. The Maintenance of Wakefulness Test is similar to the MSLT, but measures your ability to stay awake in a non-stimulating environment. Actigraphy is the continuous measurement of activity or movement over an extended period of time with the use of a device called an actigraph. An actigraph is a small, lightweight device that is typically worn on a wrist or an ankle. Actigraphy can be performed at home, which is a benefit over PSG, which typically involves an overnight stay in a sleep clinic (or related clinical facility).

Researchers are working to better understand the causes of sleep disturbance in MS. A number of possible mechanisms are being investigated, including damage to key areas of the brain that are involved in sleep. The hypothalamus is a region of the brain responsible for many of the body’s essential hormones and physiological processes. A recent study suggests that lesions in this area of the brain may cause hypersomnia and narcolepsy. The suprachiasmatic nucleus is a region of the hypothalamus responsible for maintaining our 24-hour body clock. Nerve damage to this area can make it difficult to maintain a consistent sleep-wake cycle. The brain stem is, as the name implies, the “stem-like” part of the base of the brain that is connected to the spinal cord. It plays a key role in regulating breathing and other autonomic (involuntary) nervous system functions during sleep. Research shows lesions or damage to this area can result in
sleep apnea. Damage to the hypothalamus can also disrupt key neurotransmitters involved in sleep. For example, hypocretin (also known as orexin) is an important molecule produced by the hypothalamus that helps to regulate sleep and arousal states. Abnormally low levels of hypocretin can result in narcolepsy. The hormone melatonin plays an important role in regulating sleep-wake cycles. Melatonin is produced by the pineal gland (which is regulated by the hypothalamus). Lower levels of melatonin have been associated with poor sleep quality. A recent study linked vitamin D deficiency with a higher risk of sleep disorders in the general population. Given that people with MS are more prone to vitamin D deficiency, additional research is needed to assess the relationship between vitamin D and sleep in MS.

Treating sleep disorders in MS can be quite challenging due to their many potential causes. In instances where the disturbance is secondary to a particular MS symptom (for example, urinary dysfunction or RLS), effective treatment of the sleep disorder may be obtained by remediating the underlying cause. Sedative medications may also be prescribed for short-term treatment of insomnia. Unfortunately, these drugs are often ineffective, are associated with a number of side effects, and are not recommended for long-term use. Tricyclic antidepressants are sometimes used to treat sleep disorders because they are sedating. Many people find melatonin supplements to be helpful. If used occasionally, antihistamines like Benadryl (diphenhydramine hydrochloride) can be taken for their sedating side effects. Medical equipment may also be used to treat sleep disorders. Continuous Positive Airway Pressure (CPAP) therapy is frequently used to help those struggling with sleep apnea. CPAP machines usually consist of a nosepiece or facemask connected to an air pump that delivers consistent oxygen flow to keep the airway open during sleep. A CPAP titration study is frequently done in combination with PSG to measure airflow through the nose and mouth during sleep in order to determine the appropriate therapy for each individual. Bright light therapy can be effective for treating individuals whose sleep-wake cycles are disrupted. This type of therapy is used to expose an individual’s eyes to intense, but safe, amounts of light for a specific and regular length of time. It may be delivered via a light box or light therapy glasses. Of note, it’s important to consult a physician when considering bright light therapy, as it is contraindicated in some medical conditions (such as, diabetes) and for those on certain medications (for example, melatonin or certain antibiotics).

In some cases, sleep problems can be solved without medication. Cognitive Behavioral Therapy (CBT) focuses on identifying and replacing unhelpful thoughts and behaviors with more beneficial strategies. CBT for insomnia (CBT-I) is a type of CBT that specifically focuses on identifying and changing unhelpful thoughts and behaviors that interfere with sleep. Key components of CBT-I include keeping a weekly sleep diary, using the bed only for sleep and intimacy, practicing good sleep hygiene, and using relaxation, meditation or mindfulness strategies. To cope with fatigue, people with MS often feel the need to sleep during the day. Limiting the duration of naps and taking care not to take them too close to bedtime may help one sleep more soundly at night. Many people with MS find fatigue and physical disability
often lead to decreased physical activity, however, exercise is important for regulating sleep (and it doesn’t have to be rigorous to provide benefits). According to the National Sleep Foundation, if sleep still isn’t possible after 20 minutes in bed, one should not lie awake in the middle of the night and watch the clock. This can create an unhealthy link between the sleep environment and the inability to sleep. Moving to another space to do a relaxing activity, such as reading or listening to music, before returning to bed may be more helpful.

Awareness and treatment of sleep disorders is vital for improving the health and quality of life for people living with MS. Sleep deprivation is common in people with MS, and many find their symptoms are worsened as a result. Fortunately, there are many options to help in this regard, including both behavioral and pharmaceutical remedies. Just as each individual’s journey with MS is unique, so are the solutions to any problems they may face along the way (including any sleep disorder they may be struggling with). It is very important for people with MS to discuss any concerns about the amount or quality of sleep they are getting with their healthcare team (among other things) and work with them toward the best solution.

A Highlight from ACTRIMS 2019

by David Gwynne

Last month, members of the ACP team ventured to ACTRIMS Forum 2019, in Dallas, Texas. This annual meeting focuses on the presentation of cutting edge research in MS and related demyelinating diseases.

Dr. Rhonda Voskuhl gave a wide-ranging presentation on several areas of the research from her lab at UCLA. This work included transcriptome (genetic) studies in an MS animal model, experimental autoimmune encephalomyelitis (EAE). The work used RNA sequencing to look at specific brain regions and tissues. This approach could be very useful for the discovery of pathways associated with disease, a potential source of new drug targets. Different tissues and cell types in the brain show significant heterogeneity with respect to gene expression changes during disease. A focus on astrocyte (a type of glial cell) gene expression showed differences between areas of the brain, such as cerebral cortex, cerebellum, hippocampus, and spinal cord. Pathway associated genes that showed disease related changes included genes encoding cholesterol synthesis proteins (decreased expression) and genes
encoding immune response pathway components. Cholesterol is used in the synthesis of myelin and synapses. Dr. Voskuhl is extending her work into post-mortem samples from MS patients. This work also has the potential to provide novel disability and brain atrophy-associated biomarkers.

In the second part of her presentation, Dr. Voskuhl spoke about sex differences in disease and the urgent need to examine experimental results in both males and females, from preclinical animal models to studies in clinical subjects. Steroid hormones play a significant role in these differences. This is very relevant to MS where, to quote Dr. Voskuhl, “pregnancy is good for MS” (a 70% decrease in relapses is observed in pregnant women in their third trimester). She described some experimental results where the estriol pathways were examined in gene knockout EAE mice. Estriol has neuroprotective and anti-inflammatory effects. The estriol effects are lost when the estriol receptor (beta) gene is knocked out. There are several clinical trials ongoing to look at the effects of estriol in MS, in men and women. Continuing the sex differences theme, Dr. Voskuhl made the observation that men are more likely to show a progressive disease course when compared to women. Her research results in EAE mice showed that EAE mice with an XY sex chromosome (male), vs. XX (female), showed greater clinical disease severity with more neuropathology. Her current research is looking at the mechanisms of this observation.

Interested in reading more from ACTRIMS? Dr. Farren Briggs and his team at Case Western Reserve University presented four posters at the conference. Each summarized interesting new information on such topics as the relationship between MS and comorbid autoimmune conditions, as well as risk factors for depression and disability in MS.

Repository Spotlight – the Neuroimmunological Disorders Gene-Environment Epidemiology (NDGE) Laboratory at Case Western Reserve University

Dr. Farren Briggs and his team at the NDGE Lab at Case Western Reserve University presented four posters at the 2019 ACTRIMS Forum at the end of February. Each poster summarized data from a study using ACP Repository samples and data. The team’s research uncovered interesting new information about the relationship between MS and comorbid autoimmune conditions. These studies also reveal potential risk factors for depression and disability in MS, as well as elements that may help predict an individual’s transition from relapsing remitting MS to secondary progressive forms of the disease.
The first study characterized 1,500 ACP Repository participants with MS and another autoimmune disease, as well as those with a family history of autoimmunity. For the purposes of the study, this was a representative sample of the general MS population in the United States. Subjects were classified as “polyautoimmune” if they reported having a second autoimmune disease. Data analysis showed polyautoimmunity in people with MS is greater among women, older or more educated individuals, those with a personal history of obesity, and those with a family history of autoimmunity. Interestingly, non-white people with MS were less likely to report a history of autoimmune disease than white people with MS.

The second study looked at potential risk factors for depression in MS and the ability to predict depression based on these factors. Analysis of samples and data from over 800 ACP Repository subjects revealed several non-genetic risk factors, including having a mother with a history of depression, obesity, hypertension, mononucleosis, and obstructive pulmonary disease. This study also identified genetic factors that may influence whether or not an individual with MS will develop depression at some point in the course of their disease. For example, the major alleles for the APOE gene are called E2, E3 and E4. Results from this study show that the E4 genotype is a risk factor for depression. On the other hand, the E2 genotype appears to be protective against depression. These genetic factors can easily be determined at MS onset and may potentially be used to identify those at high risk for depression.

The third poster summarized an investigation of the relationship between established MS risk factors and MS disability. This study looked at how genetic factors, such as human leukocyte antigen (HLA), and non-genetic variables, such as tobacco smoke, obesity and lower socioeconomic status, influence an individual’s level of disability. Dr. Briggs and his team concluded that genetic risk factors do not influence MS disability. As expected, older age of MS onset and longer disease duration were associated with greater disability. Male and black participants had greater disability than female and white participants, respectively. Obesity led to greater overall disability and smokers had greater deficits in walking and dexterity. Results also suggest the amount of time between an individual’s first two relapses might be an early predictor of their long-term disability outcome, with a longer interval associated with lower impairment.

The fourth study evaluated the role of both genetic and non-genetic factors in predicting an individual’s transition from relapsing remitting to secondary progressive MS (SPMS). After analyzing samples and data from over 1,200 ACP Repository subjects with MS, the study team made the following conclusions: 1) The HLA gene (specifically HLA-A*02) is highly protective against transition to SPMS such that it leads to a later transition; 2) One’s gender is a strong predictor of early transition to SPMS, with men at significantly increased risk; 3) Neurological diseases, such as migraines, are protective against transition to SPMS; and, 4) Six or more years between the first two relapses are consistently associated with a
decreased risk of and a later transition to SPMS. Understanding risk for transition to SPMS is extremely valuable to individuals affected with MS, who must plan for long-term disease management.

The ACP Repository has been an invaluable resource for these, and more that one hundred other studies. These data will be shared with and built upon by other MS researchers, advancing our understanding of the cause and effect of MS in the lives of those living with the disease. Advances such as these bring us closer to better treatments and a cure.

iConquerMS™ Spotlight – REAL MS

In the summer of 2016, the iConquerMS initiative launched REAL MS™ (Research Engagement About Life with MS), a longitudinal study of MS. REAL MS is modeled after the Framingham Heart Study, which has had a profound impact on our understanding of the causes of heart disease, as well as how to treat and prevent it. REAL MS participants complete detailed questionnaires online twice each year on a variety of subjects, including health history, diet, exercise and their experience with MS. This month, a sixth round of REAL MS surveys were released through the iConquerMS portal. The information collected through these surveys will play a pivotal role in helping scientists and clinicians gain a better understanding of the health and quality of life over time for people with MS. According to Laura Kolaczkowski, lead patient representative for iConquerMS, “REAL MS is the first time that the participants are shaping the research, and we may even unlock the answers to a cure. The power of so many of us coming together to share our experiences with MS in a way that can be measured and used by researchers can’t be overstated.” Based on the premise that “Your Health Data Has Power,” this study is just one of the many ways iConquerMS is facilitating and accelerating research on topics of importance to people affected by MS. If you are not already a member, please consider joining iConquerMS. Your voice matters! Already a member? Please log in to your account and complete your open surveys!