MAYO CLINIC

PM&R Update

Physical Medicine and Rehabilitation News Vol. 5, No. 3, 2015

INSIDE THIS ISSUE

Exploring the Connection Between Traumatic Brain Injury and Alzheimer's Disease: A Population-Based Medical Record Review Analysis

Mayo Clinic has been at the forefront of population-based epidemiological research related to both traumatic brain injury (TBI) and Alzheimer's disease and related conditions (ADRC). In May 2015, a Mayo research team was awarded a $795,000 grant by the Department of Defense to study the connection between TBI and ADRC using a population-based medical record review.

TBI causes cognitive and neurobehavioral disorders, including depression and irritability, in some individuals. Given this association, researchers speculate that TBI is also associated with an increased risk of ADRC. ADRC includes Parkinson's disease, Lewy body dementia (LBD), frontotemporal dementia and amyotrophic lateral sclerosis (ALS).

To date, epidemiological studies linking TBI and ADRC have yielded conflicting results. These findings often reflect methodological variations in defining TBI and classifying injury severity and studying clinical cohorts not representative of the broader population. Additionally, most previous analyses studying the connection between TBI and ADRC also fail to include the least severe injury category, despite the fact that epidemiological data show that this injury category is the most prevalent among both civilian and military populations.

Allen W. Brown, M.D.

According to Mayo researchers, the most accurate and reliable study design to determine whether the occurrence of TBI increases risk of the development of ADRC is to identify incident TBI events by medical record review within a defined population and classify each by injury severity, identify matched referents within that same population, and follow both cohorts over time to observe incidence rates of ADRC. Allen W. Brown, M.D., a clinical researcher and director of Brain Rehabilitation at Mayo Clinic's campus in Rochester, Minnesota, is the principal investigator of this research, and Michelle M. Mielke, Ph.D., a translational neuroepidemiologist at Mayo Clinic's campus in Minnesota, is the study's co-principal investigator.

Dr. Brown notes that this study design is unique."To the best of our knowledge, there are no published reports of a population-based analysis matching TBI cases, identified by medical record review and classified by injury severity into three strata (moderate-severe, mild, concussive), to population-based referents controlled for nonhead trauma. This is particularly important, as nonhead trauma may also increase the risk of ADRC."

Rochester Epidemiology Project

Access to the Rochester Epidemiology Project (REP) offers Mayo researchers a unique capability to study this association. The REP is a medical records linkage system that provides the infrastructure to link the medical records from all sources of care used by the population of Olmsted County, Minnesota.

Olmsted County (2010 census population, 144,248) provides a rare opportunity to investigate the epidemiological connection between TBI and ADRC. Epidemiologic research in Olmsted County is possible because the county is relatively isolated from urban centers, and because local residents receive nearly all of their medical care from a limited number of providers,

Definition of TBI based on medical record review

A confirmed event will be defined as a first TBI between Jan. 1, 1985, and Dec. 31, 1999. TBI is defined as a traumatically induced injury that contributes to the physiological disruption of brain function. Evidence in the medical record of physiological disruption includes documentation of any of the following:

- Loss of consciousness
- Post-traumatic amnesia
- Neurological signs of brain injury
- Evidence of intracerebral, subdural or epidural hematoma, cerebral or hemorrhagic contusion, or brain stem injury
- Penetrating brain injury
- Skull fracture
- Postconcussive signs and symptoms (dizziness, confusion, blurred vision, double vision, headache, nausea or vomiting) that lasted more than 30 minutes and that were not attributable to pre-existing or comorbid conditions

Information from all medical care settings will be included in this proposal (for example, hospital inpatient, hospital outpatient, emergency department, office visit or nursing home). Individuals who did not seek medical attention specifically for either the event or for sequelae (injuries identified as part of the past medical history) will be excluded since we will not have the information to confirm the TBI and the severity.

including Mayo Clinic, Olmsted Medical Center and a few private practitioners.

According to Dr. Brown, access to REP data offers two distinct advantages specific to this study. "By applying the Mayo Classification System for Traumatic Brain Injury Severity, we will have precise information on both severity and number of TBI events. These variables are believed to be important in the subsequent development of ADRC, but never before identified for this purpose by medical record review in a defined population," explains Dr. Brown.

Hypothesis

Mayo researchers hypothesize that individuals in the population with a confirmed TBI will not be at increased risk of developing ADRC compared with age- and sex-matched referents without a TBI, after controlling for nonhead injuries. Mayo researchers also suspect that they are likely to find an increased risk of developing ADRC after TBI in subsets of the cohort with clinical features that have been suspected of increasing this risk, such as multiple injuries or injuries of increased severity. If so, they hope to determine the factors that isolate that group.

Specific aims and research strategy

The Mayo research team has four specific aims:

1. Increase the size of the existing incident cohort of individuals age 30 years and older who experienced TBI between 1985 and 1999 in the population of Olmsted County, Minnesota.
2. Classify each TBI event by injury severity and determine the number of TBI events per individual.
3. Match, by age and sex, each individual with a confirmed TBI to a population-based referent without a TBI and account for nonhead trauma.
4. Longitudinally determine whether TBI, including number of events and severity, is associated with subsequent risk of ADRC after accounting for nonhead trauma.

At the conclusion of this study Mayo researchers hope to have identified and confirmed at least 2,235 individuals age 30 and older with any severity of TBI, age- and sex-matched to 2,235 population-based individuals without a TBI. Individuals will be followed from the date of the index TBI event forward until the first clinical diagnosis of an ADRC, the last medical visit in Olmsted County or death. The risk of an ADRC in those with a TBI event will be compared directly with those without a TBI event using Cox proportional hazards models and adjusting for nonhead trauma.

"These Mayo Clinic resources, along with the investigators' expertise and experience in using them to study the epidemiology of TBI and ADRC, make the proposed research novel, unique and highly likely to contribute meaningfully to the field," says Dr. Brown. "We expect this work to benefit both the military and civilian communities, providing new knowledge that will reduce the bias of previous research, and help us more accurately determine the interrelationship between TBI and subsequent development of ADRC."


Mehrsheed Sinaki, M.D., M.S.

Improving Musculoskeletal Health in Patients With Osteoporosis

Bone loss and age-related sarcopenia impair the body's ability to maintain musculoskeletal health. The body's ability to withstand extensive mechanical strain decreases with age. Improving musculoskeletal health in this population is therefore an important step in reducing the risk of fractures, falls and the significant health risks that are associated with reduced mobility.

Mehrsheed Sinaki, M.D., M.S., a physiatrist at Mayo Clinic's campus in Minnesota, initiated and spent more than 30 years evaluating the effect of muscle strength and exercise on bone mineral density, back pain and quality of life. Dr. Sinaki's numerous publications have explored the management of multiple osteoporosis-related musculoskeletal challenges, including back pain, kyphotic posture, vertebral fracture, age-related gait unsteadiness and fall prevention.

Dr. Sinaki and colleagues employ a variety of exercise programs to address these challenges. This article describes two established physical rehabilitation programs they employ and the research upon which the programs are based.

Rehabilitation of Osteoporosis Program-Exercise (ROPE)

Numerous studies have shown the positive effects of engaging in weight-bearing physical activities and confirmed that physical rehabilitative measures play a key role in preventing and managing fractures and their associated complications. Safe straining of musculoskeletal structures with proper physical activities can also reduce the risk of immobility-related deconditioning.

"Programs for preventing and managing osteoporotic fractures are designed to decrease the rate of bone resorption, improve the biomechanical competence of bone and decrease immobility," explains Dr. Sinaki. "The objective of ROPE is to improve patients' quality of life by enhancing muscle strength," says Dr. Sinaki.

A few specific research findings have guided what Dr. Sinaki and colleagues include in ROPE:

1. Improvement of back strength reduces the risk of vertebral fractures, back pain and kyphotic posture associated with osteoporosis.
2. Stronger lower extremity muscles can decrease the risk of fractures in the lower extremities.
3. Bone loss is more significant in the axial skeleton than in the appendicular skeleton.
4. Axial trabecular bone loss throughout life is higher among women than men.

Before making any exercise recommendations, Dr. Sinaki recommends performing a complete evaluation to assess the patient's physical, functional, psychological and social status, and to gauge the patient's mobility and ability to perform activities of daily living and exercise.

Depending on the baseline evaluation of the patient's musculoskeletal status, a complete exercise program typically includes weight-bearing aerobic activities for cardiovascular fitness, postural training, progressive resistance training for axial muscle and bone strengthening, stretching of soft tissues and joints, and balance training to prevent falls.

In patients with acute vertebral fractures or chronic pain after multiple vertebral fractures, the goal is to decrease pain and facilitate mobilization as quickly as possible after the fractured area is stabilized. Proper bracing of the spine and reduction of edema in the soft tissues surrounding the fractured area can help reduce pain. Early but limited use of orthotics, sedative physical therapy (heat/cold, stroking massage) and analgesics can prevent development of chronic pain syndrome. Back supports that promote muscle re-education are preferable over rigid braces. In some patients with refractory pain, kyphoplasty or vertebroplasty performed by experienced practitioners can be effective when combined with rehabilitation measures.

In a retrospective 10-year follow-up study of 50 healthy postmenopausal women published in *Bone*, Dr. Sinaki and colleagues evaluated the efficacy of ROPE as a tool for managing osteoporosis. One group of 27 women performed ROPE exercises (progressive resistive back-strengthening exercises training on the spine) for two years, while the control group of 23 did not. The researchers found that the relative risk of compression fracture in the control group subjects was 2.7 times greater than in the exercise group (Figure).

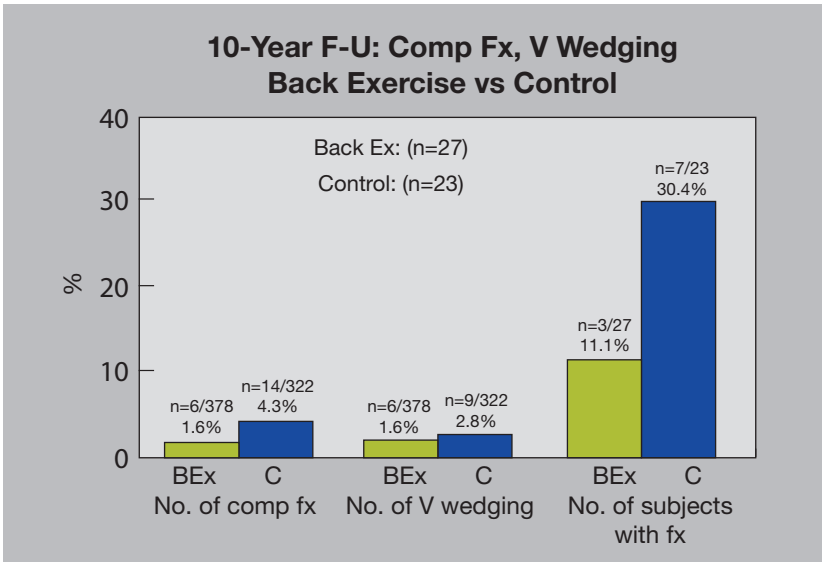

Figure. At 10-year follow-up, the incidence of vertebral compression fractures (comp fx) was 14 (4.3%) of 322 vertebral bodies examined in the control (C) group and 6 (1.6%) of 378 vertebral bodies examined in the back exercise (BEx) group (chi-square test, P = 0.0290). V, vertebral.

Graph reprinted with permission from *Osteoporosis International*. 2003;14:773. (Erratum in *Osteoporosis International*. 2006;17:1702.)

Spinal proprioceptive extension exercise dynamic (SPEED) program

Patients with kyphotic posture are at increased risk of vertebral wedging and fracture, back pain, and falls. Fear of falls and back fatigue also typically cause these patients to reduce participation in physical activities. In a study of 25 healthy, physically active women published in *Mayo Clinic Proceedings*, Dr. Sinaki and colleagues established that a four-week intervention with an inexpensive spinal weighted kypho-orthosis (WKO) and a spinal proprioceptive extension exercise dynamic (SPEED) program significantly improved patients' balance, gait and physical activity level, and reduced their back pain and risk of falls.

According to Dr. Sinaki, application of the WKO increases a patient's perception of spinal joint position, which affects dynamic and static

Mayo Clinic
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posture. Patients wore the WKO daily for one-half hour in the morning and one-half hour in the afternoon and performed a daily in-home program that included 10 repetitions of back extension exercises for reduction of kyphosis without increasing lumbar lordosis and specific proprioceptive exercises for 10 minutes twice daily to improve balance. The WKO consisted of a fitted harness with 1 kg of weight suspended on the spine between T10 and L4.

"The positive results of these interventions showed us that the SPEED program provides us with an effective tool for managing patients with kyphosis and balance disorder," says Dr. Sinaki.

For more information

Sinaki M, et al. Stronger back muscles reduce the incidence of vertebral fracture: A prospective 10-year follow-up of postmenopausal women. *Bone*. 2002;30:836.

Huntoon EA, et al. Significantly fewer refractures after vertebroplasty in patients who engage in back-extensor-strengthening exercises. *Mayo Clinic Proceedings*. 2008;83:54.

Sinaki M, et al. Significant reduction in risk of falls and back pain in osteoporotic-kyphotic women through a spinal proprioceptive extension exercise dynamic (SPEED) program. *Mayo Clinic Proceedings*. 2005;80:849.

Contact Us

Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

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Resources

MayoClinic.org/medicalprofs

Clinical trials, CME, Grand Rounds, scientific videos and online referrals

Education Opportunities

Geriatrics and orthopedics residencies for physical therapists

These yearlong post-professional clinical and didactic education training programs are designed to advance a physical therapist's preparation as a provider of patient care services. For more information: *http://www.mayo.edu/mshs/careers/physical-therapy*

25th Annual Mayo Clinic Symposium on Sports Medicine 2015

Nov. 13-14, in Rochester, Minn.
This case-oriented program provides an integrated approach to the injured athlete and includes case presentations, lectures and video demonstrations that make this course interesting to all sports medicine practitioners.

Mayo Clinic Rehabilitation Medicine Update at San Juan 2016

Feb. 5-7, 2016, in San Juan, Puerto Rico
This course is designed as an update of techniques and topics pertaining to physical medicine and rehabilitation and includes osteoporosis, amputee, ultrasound injection, cancer rehabilitation, brain injury, spinal cord injury, pain, EMG, hand and more.

Mayo Wound Symposium 2016

Feb. 18-20, 2016, in Rochester, Minn.
This course is designed to provide the latest diagnostic and treatment strategies for comprehensive wound management. Multiple educational formats will be used, including interactive workshops, hands-on demonstrations, educational sessions and case presentations that offer comprehensive wound-management strategies.

Challenges in Worker's Comp Treatment: Solutions for Complex Musculoskeletal Injuries 2016

Feb. 26, 2016, in Jacksonville, Fla.
Work-related injuries represent a unique spectrum of disease management. This course presents case-based scenarios of challenging cases that require specialty care and reviews unique treatment options.

Neurorehabilitation Summit: Regeneration, Recovery, Reintegration 2016

April 11-12, 2016, in Rochester, Minn.
This comprehensive course addresses the complex issues surrounding neurorehabilitation, including brain injury, brain rehabilitation, regeneration recovery and spinal cord injury.

Mayo Clinic Physical Medicine and Rehabilitation Board Review 2016

May 18-20, 2016, in Rochester, Minn.
This course is designed for candidates preparing for certifying and maintenance of certification examinations in physical medicine and rehabilitation and uses a combination of online learning, didactic lecture and mock oral examinations.

For more information: Visit *https://ce.Mayo.edu/physical-medicine-and-rehabilitation/pmr*, call 800-323-2688 (toll-free) or email *cme@mayo.edu*.

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