Neurologists Investigate Possible New Underlying Cause of MS

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(PhysOrg.com) -- Neurologists at the University at Buffalo are beginning a research study that could overturn the prevailing wisdom on the cause of multiple sclerosis (MS). The researchers will test the possibility that the symptoms of MS result from narrowing of the primary veins outside the skull, a condition called "chronic cerebrospinal venous insufficiency," or CCSVI.

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CCSVI is a complex vascular condition discovered and described by Paolo Zamboni, M.D., from Italy's University of Ferrara. In the original Italian patients, CCSVI was found to be strongly associated with MS, increasing the risk of developing MS by 43 fold.

This narrowing restricts the normal outflow of blood from the brain, causing alterations in the blood flow patterns within the brain that eventually causes injury to brain tissue and degeneration of neurons.

"If we can prove our hypothesis, that cerebrospinal venous insufficiency is the underlying cause of MS," said Robert Zivadinov, M.D., Ph.D., UB

associate professor of neurology, director of the Buffalo Neuroimaging Analysis Center (BNAC) and principal investigator on the study, "it is going to change the face of how we understand MS."

Michael Cain, M.D., professor and dean of the UB School of Medicine and Biomedical Sciences, said a positive outcome from this trial would have enormous implications for the treatment of MS. "Being able to identify those at risk of developing MS before symptoms take their toll could change the lives of millions of persons who now face inevitable lifestyle restrictions."

Margaret Paroski, M.D., executive vice president and chief medical officer of Kaleida Health, parent of Buffalo General Hospital where the BNAC is located, commented: "Will Rogers once said, 'It isn't what we don't know that gives us trouble, it's what we do know that ain't so'. Challenging basic assumptions about diseases has lead to some very important discoveries.

"When I was in medical school, we thought peptic ulcer disease was due to stress. We now know that 80 percent of cases are due to a bacterial infection. Dr. Zivadinov's work may lead to a whole different way of thinking about multiple sclerosis."

The preliminary findings were based on a pilot study at the BNAC headed by Zivadinov, and at the Universities of Ferrara and Bologna, Italy, directed by Zamboni and Fabrizio Salvi, M.D, respectively. The study showed that several abnormalities affecting the predominant pathways that return venous blood from the brain to the heart occurred more frequently in MS patients than in controls.

This research, supported by the Hilarescere Foundation of Italy and the BNAC, was conducted to replicate the findings of the Italian investigators.

"Results of this preliminary study, which involved 16 relapsing-remitting MS patients and eight age-and-sex-matched healthy controls, showed that all the MS patients, but none of the controls, had chronic insufficient blood flow out of the brain," said Zivadinov.

Bianca Weinstock-Guttman, M.D., UB associate professor of neurology and a co-principal investigator on the pilot study, added: "The images from this study were acquired using a method called Doppler ultrasound. The method identified anomalies in the venous blood flow associated with strictures, malformed valves and peculiar webs within the large veins of the neck and brain"

Weinstock-Guttman directs the Baird Multiple Sclerosis Center at the Jacobs Neurological Institute (JNI), UB's Department of Neurology. The JNI and BNAC are located in Buffalo General Hospital of Kaleida Health.

Advanced magnetic resonance imaging scanning (MRI) of the MS study patients conducted at the BNAC also identified distinct areas of iron deposits in the brain, and showed that those deposits may be associated with the location of MS lesions and sites of impaired drainage. The scans also revealed increased brain atrophy and changes in the flow of cerebrospinal fluid in the MS patients.

These results, which form the basis of the current larger investigation, were presented at the 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis held in September in Dusseldorf, Germany

The new study will involve 1,600 adults and 100 children. The cohort will be comprised of 1,100 patients who were diagnosed with possible or definite MS, 300 age-and-sex matched normal controls, and 300 patients with other autoimmune and neurodegenerative diseases. Enrollment in

the study has begun and will continue for two years. MS patients from across the U.S. are eligible to participate in the study.

"The prevailing wisdom that central nervous system damage in MS is predominantly the result of abnormal immune responses against the patient's nervous tissue has been challenged by research findings, which have demonstrated a significant neurodegenerative component in MS and the progressive loss of neurons" said Zivadinov.

However, these inflammatory and neurodegenerative processes occur concurrently in MS and vary considerably among patients, making it difficult to identify the cause, or causes of the disease. Consequently, the origin and development of MS remains poorly understood, and its cause remains elusive."

To determine if these preliminary findings can be repeated, Zivadinov and Weinstock-Guttman organized the present study, which will evaluate both the velocity of blood flow through both the brain's blood vessels and the extracranial veins, using Doppler ultrasound.

The technical name of the study is "combined transcranial and extracranial venous Doppler (CTEVD) evaluation in MS and related diseases".

All study subjects will undergo a general clinical examination and a Doppler scan of the head and neck to acquire images of the direction of venous blood flow in different body postures. Participants also will provide blood samples, and complete an extensive environmental questionnaire to identify potential MS risk factors.

All MS patients will undergo MRI of the brain to measure iron deposits in lesions and surrounding areas of the brain using a method called susceptibility-weighted imaging. Iron findings on these images will be

related to neuropsychological symptoms. The neuropsychological part of the study will be conducted by Ralph Benedict, Ph.D., professor of neurology and psychiatry at the JNI, UB's Department of Neurology.

A sub-cohort of 250 consecutive patients and controls will undergo MRI of the veins of the neck to confirm diagnosis of CCSVI.

Murali Ramanathan, Ph.D., associate professor in the Department of Pharmaceutical Sciences, UB School of Pharmacy and Pharmaceutical Sciences, will analyze blood samples for proteins and soluble factors associated with central nervous system injury. He also will be looking for other factors of interest in MS research, such as vitamin D metabolites and cigarette smoking, which have been linked to increased risk for developing MS as well as MS disease progression.

The data will be unblinded at three predetermined time-points, with the initial unblinding scheduled for November 2009. For more details on the study, send an email to ctevd(at)bnac.net.

Zivadinov said results of the study may lead to a larger multicenter North-American trial that will evaluate the occurrence of CCSVI in MS.

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